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<p>(54) Title: MONOCLONAL ANTIBODIES WITH REDUCED IMMUNOGENICITY</p> <p>(57) Abstract</p> <p>Antibodies having reduced immunogenicity and methods for making them are disclosed.</p>		

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MONOCLONAL ANTIBODIES WITH REDUCED IMMUNOGENICITY

This application claims the benefit of U.S. Provisional Application No. 60/083,367, filed April 28, 1998.

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Field of the Invention

This invention relates to monoclonal antibodies (mAbs) having reduced immunogenicity in humans.

10

Background of the Invention

Many potentially therapeutic mAbs are first generated in a murine hybridoma system for reasons of speed and simplicity. Non-human mAbs contain substantial stretches of amino acid sequences that will be immunogenic when injected into a human patient. It is well known that after injection of a foreign antibody, such as a murine antibody, a patient can have a strong human anti-mouse antibody (HAMA) response that essentially eliminates the antibody's therapeutic utility after the initial treatment as well as the utility of any other subsequently administered murine antibody.

Humanization techniques are well known for producing mAbs which exhibit reduced immunogenicity in humans while retaining the binding affinity of the original non-human parental mAb. See, e.g., those disclosed in U.S. Patent Nos. 5,585,089; 5,693,761; 5,693,762; and 5,225,539.

In general, these methods depend on replacing human variable heavy and light region complementarity determining regions (CDRs) with antigen specific non-human CDRs, a process known as CDR grafting. It is also well known that in CDR grafting experiments the retention of the original antigen binding affinity is enhanced and in many cases depends on choosing human acceptor framework regions that most closely match the corresponding frameworks of the CDR donor antibody.

However, since the human genome contains a limited repertoire of heavy and light chain framework regions, these methods suffer from the limitation of available human acceptor frameworks. This restriction in acceptor framework repertoire necessarily can limit the degree of match between the non-human donor and the human acceptor antibody. Thus,

5 Summary of the Invention

10 Another aspect of the invention is a method for making an antibody having reduced immunogenicity in humans comprising grafting CDRs from antigen-specific non-human antibodies onto homologous non-human primate acceptor frameworks.

Another aspect of the invention is a chimpanzee VH
20 acceptor framework IV comprising an amino acid sequence as
set forth in SEQ ID NOs: 81, 82, 83, 84 or 85.

Another aspect of the invention is a chimpanzee V κ acceptor framework IV comprising an amino acid sequence as set forth in SEQ ID NOs: 86 or 87.

Another aspect of the invention is a cynomolgus VH acceptor framework IV comprising an amino acid sequence as set forth in SEQ ID NOs: 88, 89, 90, 91, 92 or 93.

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Another aspect of the invention is a cynomolgus Vk acceptor framework IV comprising an amino acid sequence as set forth in SEQ ID NOs: 94, 95 or 96.

Yet another aspect of the invention is an isolated
5 nucleic acid molecule encoding the amino acid sequence of SEQ ID NOs: 10, 11, 12, 13, 14, 15, 16, 17, 18, 28, 29, 30, 31, 32, 33, 34, 35 or 36.

Yet another aspect of the invention is an isolated nucleic acid molecule encoding the amino acid sequence of SEQ
10 ID NOs: 81, 82, 83, 84, 85, 86 or 87.

Yet another aspect of the invention is an isolated nucleic acid molecule encoding the amino acid sequence of SEQ ID NOs: 45, 46, 47, 48, 49, 50, 51, 52, 59, 60, 61, 62, 63 or 64.

Yet another aspect of the invention is an isolated
15 nucleic acid molecule encoding the amino acid sequence of SEQ ID NOs: 88, 89, 90, 91, 92, 93, 94, 95 or 96.

Brief Description of the Drawings

20 Figure 1 is an amino acid sequence of the engineered 4A6 VL region. Asterisks above the 4A6 sequence indicate the 4A6 framework residues retained in the engineered molecule. Bold and italicized letters indicate the CDRs.

Figure 2 is an amino acid sequence of the engineered 4A6
25 VH region. Asterisks above the 4A6 sequence indicate the 4A6 framework residues retained in the engineered molecule. Bold and italicized letters indicate the CDRs.

Figure 3 is an amino acid sequence alignment comparing the murine antibody B9VK with the closest matching chimpanzee
30 Vk and selected Jk sequences. The CDR regions are indicated by bold and italicized letters. Gaps are indicated by dots. The numbering convention is from Kabat et al., *infra*.

Figure 4 is an amino acid sequence alignment comparing the murine antibody B9VH with the closest matching chimpanzee
35 VH and selected JH sequences. The CDR regions are indicated by bold and italicized letters. Gaps are indicated by dots. Asterisks indicate framework residues that are predicted to interact with CDRs and affect antigen binding affinity. The numbering convention is from Kabat et al., *infra*.

Figure 5 is an amino acid sequence alignment comparing the murine antibody 3G9VK with the closest matching chimpanzee VK and selected Jk sequences. The CDR regions are indicated by bold and italicized letters. Gaps are indicated by dots. Asterisks indicate framework residues that are predicted to interact with CDRs and affect antigen binding affinity. The numbering convention is from Kabat et al., *infra*.

Figure 6 is an amino acid sequence alignment comparing the murine antibody 3G9VH with the closest matching chimpanzee VH and selected JH sequences. The CDR regions are indicated by bold and italicized letters. Gaps are indicated by dots. Asterisks indicate framework residues that are predicted to interact with CDRs and affect antigen binding affinity. The numbering convention is from Kabat et al., *infra*.

Detailed Description of the Invention

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as though fully set forth.

The molecular genetic aspects of antibody structure have been reviewed by S. Tonegawa in *Nature* 302:575-581 (1983). Briefly, antibodies are heterodimers comprised of at least two heavy and two light chains. The N-terminal domain of each heavy and light chain, termed VH and VL, respectively, fold together to form the antigen combining site. On the genetic level, the VL domain is encoded by two different gene segments, termed VK or V_L, and JK or J_L that join together to form one continuous VL region. Similarly, the VH domain is encoded by three gene segments, VH, DH, and JH, that join together to form one continuous VH region. Thus different VL and VH regions may be encoded by different combinations of VK or V_L, JK or J_L and VH, DH, and JH. This combinatorial diversity is in part the means by which the immune response generates the myriad diversity of different antibody molecules and their associated antigen specificities.

On the protein level, each heavy and light V region domain may be further divided into three CDRs. Three heavy

and three light chain CDRs fold together to form the antigen binding surface and part of the underlying support structures that are required to maintain the exact three-dimensional structure of the antigen combining site. Flanking each CDR are framework regions that in most cases do not directly interact with the specific antigen, but rather serve to form the scaffold which supports the antigen binding properties of the CDRs. Each heavy and light chain has four framework regions, three derived from the VH or VL gene segment, the fourth is derived from the JH, JK, or J_L gene segment. Thus, the order of frameworks and CDRs from the N- terminus is framework I, CDRI, framework II, CDRII, framework III, CDRIII, framework IV. On the genetic level, all of framework I through Framework III is encoded by the V region gene segment; CDRIII is encoded jointly by both the V region and J region gene segments; framework IV is encoded entirely from the J gene segment.

As used herein, "antibodies" refers to immunoglobulins and immunoglobulin fragments lacking all or part of an immunoglobulin constant region, e.g., Fv, Fab, Fab' or F(ab')₂ and the like.

The term "donor antibody" refers to a monoclonal or recombinant antibody which contributes the nucleic acid sequences of its variable regions, CDRs or other functional fragments or analogs thereof to an engineered antibody, so as to provide the engineered antibody coding region and resulting expressed engineered antibody with the antigenic specificity and neutralizing activity characteristic of the donor antibody.

The term "acceptor antibody" refers to monoclonal or recombinant antibodies heterologous to the donor antibody, which contributes all, or a portion, of the nucleic acid sequences encoding its heavy and/or light chain framework regions and/or its heavy and/or light chain constant regions or V region subfamily consensus sequences to the engineered antibody.

A "functional fragment" is a partial heavy or light chain variable sequence (e.g., minor deletions at the amino or carboxy terminus of the immunoglobulin variable region)

which retains the same antigen binding specificity and affinity as the antibody from which the fragment was derived.

An "analog" is an amino acid sequence modified by at least one amino acid, wherein said modification can be chemical or a substitution, which modification permits the amino acid sequence to retain the biological characteristics, e.g., antigen specificity and high affinity, of the unmodified sequence.

Methods are provided for making engineered antibodies with reduced immunogenicity in humans and primates from non-human antibodies. CDRs from antigen-specific non-human antibodies, typically of rodent origin, are grafted onto homologous non-human primate acceptor frameworks. Preferably, the non-human primate acceptor frameworks are from Old World apes. Most preferably, the Old World ape acceptor framework is from *Pan troglodytes*, *Pan paniscus* or *Gorilla gorilla*. Particularly preferred is the chimpanzee *Pan troglodytes*. Also preferred are Old World monkey acceptor frameworks. Most preferably, the Old World monkey acceptor frameworks are from the genus *Macaca*. Particularly preferred is the cynomolgus monkey *Macaca cynomolgus*.

Particularly preferred chimpanzee (*Pan troglodytes*) heavy chain variable region frameworks (VH) are CPVH41-12 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 10 and the framework IV amino acid sequence shown in SEQ ID NO: 83; CPVH41-1 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 11 and the framework IV amino acid sequence shown in SEQ ID NO: 85; CPVH41-4 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 12; CPVH41-7 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 13; CPVH41-8 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 14, CPVH41-9 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 15 and the framework IV amino acid sequence shown in SEQ ID NO: 81; CPVH41-10 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 16 and the framework IV amino acid sequence shown in SEQ ID NO: 82; CPVH41-18 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 17; and CPVH41-19 having the framework I, II and III

amino acid sequence shown in SEQ ID NO: 18 and the framework IV amino acid sequence shown in SEQ ID NO: 84.

Particularly preferred chimpanzee (*Pan troglodytes*) light chain kappa variable region frameworks (VK) are CPVK46-1
5 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 28; CPVK46-3 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 29; CPVK46-4 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 30; CPVK46-5 having the framework I, II and III amino
10 acid sequence shown in SEQ ID NO: 31; CPVK46-6 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 32 and the framework IV amino acid sequence shown in SEQ ID NO: 86; CPVK46-7 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 33 and the framework IV
15 amino acid sequence shown in SEQ ID NO: 87; CPVK46-8 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 34; CPVK46-11 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 35; and CPVK46-14 having the framework I, II and III amino acid sequence shown in SEQ
20 ID NO: 36.

Particularly preferred cynomolgus (*Macaca cynomolgus*) heavy chain variable region frameworks (VH) are CYVH2-1
having the framework I, II and III amino acid sequence shown in SEQ ID NO: 45 and the framework IV amino acid sequence
25 shown in SEQ ID NO: 88; CYVH2-3 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 46 and the framework IV amino acid sequence shown in SEQ ID NO: 89; CYVH2-4 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 47 and the framework IV amino
30 acid sequence shown in SEQ ID NO: 90; CYVH2-5 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 48 and the framework IV amino acid sequence shown in SEQ ID NO: 93; CYVH2-6 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 49 and the framework IV
35 amino acid sequence shown in SEQ ID NO: 91; CYVH2-7 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 50; CYVH2-8 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 51; and CYVH2-10 having the

framework I, II and III amino acid sequence shown in SEQ ID NO: 52 and the framework IV amino acid sequence shown in SEQ ID NO: 92.

Particularly preferred cynomolgus (*Macaca cynomolgus*)

5 light chain kappa variable region frameworks (Vk) are CYVk4-2 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 59; CYVk4-3 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 60 and the framework IV amino acid sequence shown in SEQ ID NO: 94; CYVk4-5 having
10 the framework I, II and III amino acid sequence shown in SEQ ID NO: 61; CYVk4-6 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 62 and the framework IV amino acid sequence shown in SEQ ID NO: 95; CYVk4-10 having the framework I, II and III amino acid sequence shown in SEQ
15 ID NO: 63; and CYVk4-11 having the framework I, II and III amino acid sequence shown in SEQ ID NO: 64 and the framework IV amino acid sequence shown in SEQ ID NO: 96.

Isolated nucleic acid molecules encoding the chimpanzee VH and Vk acceptor framework I, II and III amino acid
20 sequences of SEQ ID NOS: 10, 11, 12, 13, 14, 15, 16, 17, 18, 28, 29, 30, 31, 32, 33, 34, 35 or 36 and the framework IV amino acid sequences of SEQ ID NOS: 81, 82, 83, 84, 85, 86 or 87 are also part of the present invention. Further, isolated nucleic acid molecules encoding the cynomolgus VH and Vk
25 acceptor framework I, II and III amino acid sequences of SEQ ID NOS: 45, 46, 47, 48, 49, 50, 51, 52, 59, 60, 61, 62, 63 or 64 and the framework IV amino acid sequences of SEQ ID NOS: 88, 89, 90, 91, 92, 93, 94, 95 or 96 are also part of the present invention. Nucleic acid sequences encoding
30 functional fragments or analogs of the VH and Vk acceptor framework amino acid sequences are also part of the present invention.

In addition to isolated nucleic acid sequences encoding VH and Vk acceptor frameworks described herein, nucleic acid
35 sequences complementary to these framework regions are also encompassed by the present invention. Useful DNA sequences include those sequences which hybridize under stringent hybridization conditions to the DNA sequences. See, T.

Maniatis et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory (1982), pp. 387-389. An example of one such stringent hybridization condition is hybridization at 4XSSC at 65°C, followed by a washing in

5 0.1XSSC at 65°C for one hour. Alternatively, an exemplary stringent hybridization condition is 50% formamide, 4XSSC at 42°C. Preferably, these hybridizing DNA sequences are at least about 18 nucleotides in length.

Suitable frameworks are selected by computer homology
10 searching among members of a database of Old World ape or monkey VH and VL regions. The framework portions of primate antibodies are useful as components of therapeutic antibodies. Moreover, primate antibody frameworks will be tolerated when used in the treatment of humans due to the
15 close sequence homology between the genes of the primates and humans. Thus, the present invention provides for the grafting of CDRs from an antigen specific non-human donor antibody to acceptor V regions derived from non-human primate species.

20 The antigen specificity and binding kinetics of the donor antibody, which may be of rodent or any other non-human origin, are best preserved by selecting primate acceptor V regions that are determined by computer homology searching to be most similar to the donor antibody. Alternatively, the
25 acceptor antibody may be a consensus sequence generated from primate V region subfamilies, or portions thereof, displaying the highest homology to the donor antibody.

The resulting engineered constructs, in which the donor CDRs are grafted onto primate acceptor frameworks, are
30 subsequently refined by analysis of three-dimensional models based on known antibody crystal structures as found, e.g., in the Protein Data Bank, <http://www.pdb.bnl.gov/pdb-bin/pdbmain>. Alternatively, computer generated three-dimensional models of the donor antibody may be computed by
35 means of commercially available software such as "AbM" (Oxford Molecular, Oxford, UK).

Structural analysis of these models may reveal donor framework residues that are CDR-contacting residues and that are seen to be important in the presentation of CDR loops,

and therefore binding avidity. A CDR-contacting residue is one which is seen in three-dimensional models to come within the van der Waals radius of a CDR residue, or could interact with a CDR residue via a salt bridge or by hydrophobic interaction. Such donor framework (CDR-contacting) residues may be retained in the engineered construct.

The modeling experiments can also reveal which framework residues are largely exposed to the solvent environment. The engineered constructs may be further improved by substituting some or all of these solvent-accessible amino acid residues with those found at the same position among human V regions most homologous to the engineered construct as disclosed in U.S. Patent No. 5,639,641.

The engineered V regions are then joined to one or more different human or Old World ape constant regions depending on the desired secondary immune functions such as complement fixation or Fc receptor binding. Human constant regions can be selected from human immunoglobulin classes and isotypes, such as IgG (subtypes 1 through 4), IgM, IgA, and IgE. An IgG4 subtype variant containing the mutations S228P and L235E (PE mutation) in the heavy chain constant region which results in reduced effector function can also be selected. See U.S. Patent Nos. 5,624,821 and 5,648,260.

The complete heavy and light chain genes are transferred to suitable expression vectors and co-expressed in the appropriate host cells such as chinese hamster ovary, COS or myeloma cells. The resulting engineered antibody is expected to be of substantially reduced immunogenicity when administered to humans, and to retain full binding affinity for antigen.

Acceptor V regions can be isolated specifically for each donor V region by directed PCR methodology where a non-human primate cDNA library is surveyed for acceptor frameworks most similar to the donor antibody. Oligonucleotide PCR primers homologous to the donor antibody framework I (paired with C-region 3' PCR primers) are used to direct PCR amplification of a non-human primate, e.g., chimpanzee lymphocyte cDNA library. This would select for V-regions with framework I regions similar to the donor antibody, and sequence analysis of the obtained clones would reveal the associated framework

II and III (and IV) sequences. 3' PCR primers would then be designed based on the knowledge of the non-human primate framework III sequences thus obtained, and used to direct PCR amplification of the original cDNA library together with a vector-specific 5' PCR primer. cDNA clones obtained from the second round of PCR amplification would have framework I and III sequences most similar to the donor antibody, and the framework II sequences would display a similar degree of sequence homology.

10

The present invention will now be described with reference to the following specific, non-limiting examples.

Example 1

Random cDNA Cloning and Sequence Analysis of Chimpanzee VH Regions

Five ml of peripheral blood was collected and pooled from three chimpanzees (*Pan troglodytes*) and peripheral blood mononuclear cells were isolated by standard density centrifugation methods. These cells, which include antibody producing lymphocytes, were dissolved in TRIzol reagent (GIBCO, Gaithersburg, MD, USA) and total RNA was recovered from this material by solvent extraction and precipitation according to the manufacturer's specifications.

Chimpanzee heavy chain V regions were cloned from the total RNA using Marathon RACE methodology (Clontech, Palo Alto, CA, USA) following exactly the manufacturer's protocol using 3' Cg1 gene specific primers. After RACE PCR amplification, DNA bands of the expected size were excised from agarose gels, the DNA was purified and cloned into a plasmid vector. Although this cDNA library contains many distinct heavy chain V region clones, nine were selected randomly for sequence analysis. Complete nucleic acid sequences and predicted protein sequences of the chimpanzee VH cDNA clones 41-12, 41-1, 41-4, 41-7, 41-8, 41-9, 41-10, 41-18 and 41-19 are shown in SEQ ID NOS: 1, 2, 3, 4, 5, 6, 7, 8 and 9, respectively. The amino acid sequences of the region from the first amino acid of the mature VH region to the second conserved cysteine residue at position 92, adjacent to CDR III of these clones, namely, CPVH41-12,

CPVH41-1, CPVH41-4, CPVH41-7, CPVH41-8, CPVH41-9, CPVH41-10, CPVH41-18 and CPVH41-19 are shown in SEQ ID NOs: 10, 11, 12, 13, 14, 15, 16, 17 and 18, respectively. The amino acid sequence of the region encoding framework IV of these clones
 5 for CPVH41-9, CPVH41-10, CPVH41-12, CPVH41-19 and CPVH 41-1 are shown in SEQ ID NOs: 81, 82, 83, 84 and 85, respectively.

The chimpanzee VH amino acid sequences from the mature N-terminus and the second conserved cysteine residue at position 92, adjacent to CDRIII, were used as query sequences
 10 in computer homology searching of the Kabat database of Sequences of Proteins of Immunological Interest (ftp://ncbi.nlm.nih.gov/repository/kabat/) The results of this analysis are shown in Table 1.

In each case, the closest match was with a human VH
 15 region, displaying between 76% (41-1/HHC20G) and 94% (41-10/HHC20Y) sequence identity at the amino acid level. Matches were found for each of the three major human VH subgroups, indicating that the chimpanzee VH repertoire includes at least some members homologous to each of the
 20 major human subgroups. The human subgroup homology is presented in Table 1.

Table 1			
	Clone	Closest Match	Overall Amino Acid Homology
25	41-4	HHC10X	88%
	41-9	HHC10Y	92
	41-18	HHC10D	84
30	41-1	HHC20G	76
	41-10	HHC20Y	94
	41-12	HHC20C	83
	41-7	HHC30T	80
	41-8	HHC30T	79
35	41-19	HHC30S	82
			VH Subgroup Match
			I
			I
			I
			II
			II
			II
			III
			III
			III

The results show that the overall sequence identity between the chimpanzee and human VH regions ranged between 76 and 95% with a mean identity of 84%. Based on this
 40 observation, further sampling of the chimpanzee random VH library will likely provide a substantially greater diversity of VH sequences from which to choose optimum acceptor frameworks for each particular donor VH region.

Example 2Random cDNA Cloning and Sequence Analysis of Chimpanzee VK
Regions

Chimpanzee light chain VK regions were cloned from the
5 total RNA using Marathon RACE methodology (Clontech, Palo
Alto, CA, USA) following exactly the manufacturer's protocol
and Cκ 3' gene specific primers. After RACE PCR
amplification, DNA bands of the expected size were excised
from agarose gels, the DNA was purified and cloned into a
10 plasmid vector. Although this cDNA library contains many
distinct light chain VK region clones, nine were selected
randomly for sequence analysis. Complete nucleic acid
sequences and predicted protein sequences of the chimpanzee
VK cDNA clones 46-1, 46-3, 46-4, 46-5, 46-6, 46-7, 46-8, 46-
15 11 and 46-14 are shown in SEQ ID NOs: 19, 20, 21, 22, 23, 24,
25, 26 and 27, respectively. The amino acid sequences of the
region from the first amino acid of the mature VK region to
the second conserved cysteine residue at position 88,
adjacent to CDR III of these clones, namely CPVK46-1, CPVK46-
20 3, CPVK46-4, CPVK46-5, CPVK46-6, CPVK46-7, CPVK46-8, CPVK46-11
and CPVK46-14 are shown in SEQ ID NOs: 28, 29, 30, 31, 32,
33, 34, 35 and 36, respectively. The amino acid sequences of
the region encoding framework IV of these clones for CPVK46-6
and CPVK46-7 are shown in SEQ ID NOs: 86 and 87,
25 respectively.

The chimpanzee VK amino acid sequences comprising the
mature N-terminus and the second conserved cysteine residue
at position 88 were used as query sequences in computer
homology searching of the Kabat database. The results of
30 this analysis are shown in Table 2. In each case the closest
match was with a human VK region, displaying between 68%
(46-4/HKL310) and 97% (46-11/HKL106) sequence identity at the
amino acid level. It is evident that the chimpanzee VK
sequences are distinct from the collection of human VK found
35 in the Kabat database.

The human subgroup homology is presented in Table 2. Of the four major human Vk subgroups, matches were found for the two most frequently isolated, indicating that the chimpanzee Vk repertoire is at least homologous to members of the majority of the human Vk repertoire. Further sampling of the chimpanzee Vk cDNA library will likely identify a greater diversity of chimpanzee Vk regions, including ones homologous to the remaining two human Vk subgroups (VkII and VkIV).

Table 2			
		Overall Amino	
Clone	Closest Match	Acid Homology	VH Subgroup Match
46-1	HKL10C	85%	I
46-3	HKL 100	91	I
46-5	HKL 100	91	I
46-7	HKL 100	81	I
46-8	HKL 10N	90	I
46-11	HKL 106	97	I
46-14	HKL 100	92	I
46-4	HKL 310	68	III
46-6	HKL 310	96	III

Example 3

Random cDNA Cloning and Sequence Analysis of Cynomolgus VH Regions

Splenic RNA was recovered from a single donor cynomolgus monkey (*Macaca cynomolgus*) by means of standard laboratory practice. Cynomolgus heavy chain V regions were cloned from the total RNA using Marathon RACE methodology (Clontech, Palo Alto, CA, USA) following exactly the manufacturer's protocol using 3' C γ 1 gene specific primers. After RACE PCR amplification, DNA bands of the expected size were excised from agarose gels, the DNA was purified and cloned into a plasmid vector. Although this cDNA library contains many distinct heavy V region clones, eight were selected randomly for sequence analysis. Complete nucleic acid sequences and predicted protein sequences of the Cynomolgus VH cDNA clones 2-1, 2-3, 2-4, 2-5, 2-6, 2-7, 2-8 and 2-10 are shown in SEQ ID NOs: 37, 38, 39, 40, 41, 42, 43 and 44, respectively. The amino acid sequences of the region from the first amino acid of the mature VH region to the second conserved cysteine residue at position 92, adjacent to CDR III of these clones, namely CyVH2-1, CyVH2-3, CyVH2-4, CyVH2-5, CyVH2-6, CyVH2-7, CyVH2-8 and CyVH2-10 are shown in SEQ ID NOs: 45, 46, 47, 48,

49, 50, 51 and 52, respectively. The amino acid sequences of the region encoding framework IV of these clones for CyVH2-1, CyVH2-3, CyVH2-4, CyVH2-6, CyVH2-10 and CyVH2-5 are shown in SEQ ID NOs: 88, 89, 90, 91, 92 and 93, respectively.

5 The cynomolgus VH amino acid sequences from the mature N-terminus and the second conserved cysteine residue at position 92, adjacent to CDRIII, were used as query sequences in computer homology searching of the Kabat database. The results of this analysis are shown in Table 3. In each case
10 the closest match was with a human VH region, displaying between 62% (2-6/ HHC20E) and 84% (2-5/ HHC20F) sequence identity at the amino acid level. It is evident that the cynomolgus VH sequences are distinct from the collection of human VH found in the Kabat database. Matches were found for
15 each of the three major human VH subgroups, indicating that the cynomolgus VH repertoire includes at least some members homologous to each of the major human subgroups. The human subgroup homology is presented in Table 3.

20

Table 3
Overall Amino

Clone	Closest Match	Acid Homology	VH Subgroup Match
2-4	HHC10Y	83%	I
2-10	HHC20G	83	II
25 2-8	HHC20F	74	II
2-6	HHC20E	62	II
2-5	HHC20F	84	II
2-3	HHC20F	75	II
2-1	HHC316	71	III
30 2-7	HHC31C	81	III

The results show that the overall sequence identity between the cynomolgus and human VH regions ranged between 62 and 84% with a mean identity of 77%. Based on this
35 observation, further sampling of the cynomolgus random VH library will likely provide a substantially greater diversity of VH sequences from which to choose optimum acceptor frameworks for each particular donor VH region.

40

Example 4**Random cDNA Cloning and Sequence Analysis of Cynomolgus V κ** **Regions**

Cynomolgus light chain V κ regions were cloned from the total splenic RNA using Marathon RACE methodology (Clontech,

Palo Alto, CA, USA) following exactly the manufacturer's protocol and Ck 3' gene specific primers. After RACE PCR amplification, DNA bands of the expected size were excised from agarose gels, the DNA was purified and cloned into a plasmid vector. Although this cDNA library contains many distinct light chain Vk region clones, six were selected randomly for sequence analysis. Complete nucleic acid sequences and predicted protein sequences of the Cynomolgus Vk cDNA clones 4-2, 4-3, 4-5, 4-6, 4-10 and 4-11 are shown in SEQ ID NOs: 53, 54, 55, 56, 57 and 58, respectively. The amino acid sequences of the region from the first amino acid of the mature Vk region to the second conserved cysteine residue at position 88, adjacent to CDRIII, of these clones, namely CyVk4-2, CyVk4-3, CyVk4-5, CyVk4-6, CyVk4-10 and CyVk4-11 are shown in SEQ ID NOs: 59, 60, 61, 62, 63 and 64, respectively. The amino acid sequences encoding the framework IV region of these clones for CyVk4-3, CyVk4-6 and CyVk4-11 are shown in SEQ ID NOs: 94, 95 and 96, respectively.

The cynomolgus Vk amino acid sequences comprising the mature N-terminus and the second conserved cysteine residue at position 88 were used as query sequences in computer homology searching of the Kabat database. The results of this analysis are shown in Table 4. In each case the closest match was with a human Vk region, displaying between 73% (4-11/ HKL10S) and 94% (4-3/ HKL400) sequence identity at the amino acid level. It is evident that the cynomolgus Vk sequences are distinct from the collection of human Vk found in the public genetic databases. The human subgroup homology is presented in Table 4. Matches were found for three of the four major human Vk subgroups, indicating that the cynomolgus Vk repertoire is largely homologous to members of the majority of the human Vk repertoire. Further sampling of the cynomolgus Vk cDNA library will likely identify a greater diversity of cynomolgus Vk regions, including ones homologous to the remaining human Vk subgroup (VKIII).

Table 4
Overall Amino

	Clone	Closest Match	Acid Homology	Vk Subgroup Match
5	4-6	HKL10L	80%	I
	4-2	HKL10Z	83	I
	4-11	HKL10S	73	I
	4-10	HKL10F	93	I
	4-5	HKL209	86	II
10	4-3	HKL400	94	IV

The results show that the overall sequence identity between the cynomolgus and human Vk regions ranged between 73 and 94% with a mean identity of 85%. Based on this

observation, further sampling of the cynomolgus random Vk library will provide a substantially greater diversity of Vk sequences from which to choose optimum acceptor frameworks for each particular donor Vk region.

Example 5

Preparation of Engineered Anti-IL-5 Monoclonal Antibodies

The Vk and VH genes of the rat anti-interleukin-5 (IL-5) antibody 4A6 are shown in SEQ ID NOs: 65 and 66, respectively. These genes encode a high affinity neutralizing monoclonal antibody specific for human IL-5 useful for the treatment of asthma. See U.S. Patent No. 5,693,323.

The 4A6 light chain was engineered as follows. The sequence of donor antibody Vk4A6 (SEQ ID NO: 65) was aligned with the acceptor antibody light chain Vk region from the chimpanzee Mab C108G (*Mol. Immunol.* 32:1081-1092 (1995)) (SEQ ID NO: 67) as shown in Fig. 1. Since native Vk4A6 has a unique deletion of residue 10, the sequence alignment included the insertion of a gap at that position. The CDR residues were identified as defined by the convention of Kabat et al. in *Sequences of Proteins of Immunological Interest*, 4th ed., U.S. Department of Health and Human Services, National Institutes of Health (1987).

Framework residues that could influence CDR presentation were identified by analysis of three-dimensional models based on known antibody crystal structures. The residues of this

CDR-contacting set were compared among the aligned Vk4A6 and Vkc108G sequences, and the positions of the set that differed between the Vk4A6 and the Vkc108G were marked (Fig. 1, asterisks). The CDRs and the marked framework residues of 5 Vk4A6 (the donor antibody) were transferred replacing the corresponding residues of Vkc108G (the acceptor antibody). The completed engineered 4A6 light chain V region is shown in SEQ ID NO: 68. Six donor framework residues were retained in the engineered molecule at residues 1 to 4, 49 and 60.

10 In analogous fashion, a similar method was used to engineer the 4A6 heavy chain. The sequence of donor antibody VH4A6 (SEQ ID NO: 66) was aligned with the acceptor antibody heavy chain V region from the chimpanzee Mab C108G (SEQ ID NO: 69) as shown in Fig. 2. A large gap was introduced in 15 the VH4A6 CDRIII alignment, as CDRIII of VHC108G is 10 residues longer. CDR residues were identified as defined by the convention of Kabat et al., *supra*.

Framework residues that could influence CDR presentation were identified by analysis of three-dimensional models based 20 on known antibody crystal structures. The residues of this CDR-contacting set were compared among the aligned VH4A6 and VHC108G sequences, and the positions of the set that differed between the VH4A6 and the VHC108G were marked (Fig. 2, asterisks). In total, 11 such CDR contacting residues that 25 differed between VH4A6 and the VHC108G were selected and marked. The CDRs and the marked CDR contacting framework residues of VH4A6 (the donor antibody) were transferred replacing the corresponding residues of VHC108G (the acceptor antibody). The completed engineered 4A6 heavy chain V region 30 is shown in SEQ ID NO: 70. Eleven donor framework residues were retained in the engineered molecule at residues 27, 30, 38, 49, 66, 67, 69, 71, 73, 78 and 94.

The engineered 4A6 can be expressed in cells using methods well known to those skilled in the art. Briefly, 35 genes encoding the complete engineered 4A6 VH and Vk regions can be assembled from long synthetic oligonucleotides and ligated into appropriate eukaryotic expression vectors containing the desired antibody constant regions. Such an expression vector will contain selectable markers, for

example, neomycin resistance and regulatory sequences, for example, the CMV promoter, required to direct the expression of full-length antibody heavy and light chains. Subsequently, transfection of the appropriate host cell, for example, chinese hamster ovary, would result in the expression of fully active engineered 4A6.

Example 6

Preparation of Engineered Anti-Integrin Monoclonal Antibodies

10 The V_K and V_H genes of the murine anti-integrin antibody B9 are shown in SEQ ID NOs: 71 and 72, respectively. These genes encode a high affinity neutralizing monoclonal antibody specific for human integrin $\alpha v \beta 3$ useful for the treatment of vascular diseases.

15 The B9 light chain was engineered as follows. The amino acid sequence of donor antibody V_KB9 (SEQ ID NO: 72) was compared to each of the nine chimpanzee V_K sequences described above and percent sequence identity determined by computer homology searching using the LASERGENE program "MEGALIGN" (DNASTAR, Inc., Madison, WI). Clones CPV_K46-3 (SEQ ID NO: 29) and CPV_K46-14 (SEQ ID NO: 36) were identified as the chimpanzee V_K regions with the highest overall sequence similarity (77%) to the B9 donor V_K. CPV_K46-3 was selected as the acceptor framework.

25 Similarly, the chimpanzee J_K gene segment of CPV_K46-1 (SEQ ID NO: 97) was selected as acceptor framework IV. The sequences of the donor V_KB9 and acceptor CPV_K46-3, CPV_K46-1 V regions were aligned and the positions of their respective framework and CDRs were determined as shown in Fig. 3.

30 The CDR residues were identified as defined by the convention of Kabat et al., *supra*. The results show that V_KB9 and CPV_K46-3 share 77% overall sequence identity, with the framework regions I through III sharing 81% sequence identity.

35 Framework residues that could influence CDR presentation were identified by analysis of three-dimensional models based on known antibody crystal structures. The residues of this

CDR-contacting set were compared among the aligned VkB9 and CPVk46-3 sequences, and none of this set were found that differed between the VkB9 and the CPVk46-3. Accordingly, only the CDRs of VkB9 (the donor antibody) were transferred replacing the corresponding residues of CPVk46-3 (the acceptor antibody). Lastly, the framework IV sequences of CPVk46-1 replaced the corresponding framework IV residues of the B9 light chain variable region. The completed engineered B9 light chain V region is shown in SEQ ID NO: 73. No donor framework residues were retained in the engineered light chain variable region.

The B9 heavy chain was engineered in analogous fashion. The amino acid sequence of donor antibody VHB9 (SEQ ID NO: 71) was compared to each of the nine chimpanzee VH sequences described above by computer homology searching. Clone CPVH41-18 (SEQ ID NO: 17) was identified as the chimpanzee VH region with the highest overall sequence similarity (58%) to the B9 donor VH.

The chimpanzee JH gene segment of CPVH41-10 (SEQ ID NO: 82) was selected as acceptor framework IV. The sequences of the donor VHB9 and chimpanzee acceptor V regions were aligned and the positions of their respective framework and CDRs determined as shown in Fig. 4.

The CDR residues were identified as defined by the convention of Kabat et al., *supra*. The results show that VHB9 and CPVH41-18 share 58% overall sequence identity, with the framework regions I through III sharing 65% sequence identity.

Framework residues that could influence CDR presentation were identified by analysis of three-dimensional models based on known antibody crystal structures. The residues of this CDR-contacting set were compared among the aligned VHB9 and CPVH41-18 sequences, and the nine residues of the set that differed between VHB9 and the chimpanzee acceptor frameworks were marked. The CDRs and the marked framework residues of donor antibody VHB9 were transferred replacing the corresponding residues of CPVH41-18 (the acceptor antibody). Lastly, the framework IV sequences of CPVH41-10 replaced the corresponding framework IV residues of the B9 heavy chain variable region. The completed engineered B9 heavy chain V

region is shown in SEQ ID NO: 74. Nine donor framework residues were retained in the engineered heavy chain variable region at positions 24, 27, 38, 48, 66, 67, 69, 93 and 94.

5

Example 7

Expression and Characterization of Engineered Anti-Integrin Monoclonal Antibodies

The engineered B9 antibody was expressed in cells using methods well known to those skilled in the art. Briefly, genes encoding the complete engineered B9 VH and VK regions were assembled from long synthetic oligonucleotides and ligated into appropriate eukaryotic expression vectors containing IgG1_K antibody constant regions. The expression vector contained a selectable marker for neomycin resistance and CMV promoter regulatory sequences. Subsequent transfection of a COS host cell resulted in the expression of engineered B9 (CPB9).

The relative binding avidity of CPB9 was compared to that of the original murine B9 antibody as follows. CPB9 antibodies present in culture supernatants from cells maintained in culture for 5 days after transfection with the expression constructs were compared to the parental murine B9 antibody using the ORIGEN technology (IGEN Inc, Gaithersburg, MD). Briefly, different dilutions of the B9 variants were incubated with purified human $\alpha\text{v}\beta 3$ integrin which had previously been biotinylated, and an electrochemiluminescent TAG moiety specific for the antibody C regions. B9 variant antibody bound to the integrin was measured by capturing the immune complexes onto streptavidin beads followed by analysis on the ORIGEN instrument. The results showed that the CPB9 and the murine B9 binding curves were displaced only by about 3-fold indicating that the overall specific binding avidity of CPB9 and murine B9 for $\alpha\text{v}\beta 3$ are within three-fold of each other. Accordingly, the results show that the CDR grafting of rodent CDRs onto chimpanzee frameworks as described in the present invention retained nearly all of the binding avidity of the parent rodent mAb.

Example 8Preparation of Engineered Anti-Erythropoietin Receptor
Monoclonal Antibodies

5 The VH and Vk genes of the murine anti-erythropoietin
receptor antibody 3G9 are shown in SEQ ID NOs: 75 and 76,
respectively. These genes encode a high affinity
neutralizing monoclonal antibody specific for human
erythropoietin receptor (EPOR) useful for the treatment of
hematopoietic disorders.

10 The 3G9 light chain was engineered as follows. The
amino acid sequence of donor antibody Vk3G9 (SEQ ID NO: 76)
was compared to each of the nine chimpanzee Vk sequences
described above by computer homology searching as described
above. Clones CPVk46-3 (SEQ ID NO: 29), CPVk46-5 (SEQ ID NO:
15 31), CPVk46-8 (SEQ ID NO: 34) and CPVk46-14 (SEQ ID NO: 36)
were identified as the chimpanzee Vk regions with the highest
overall sequence similarity (65%) to the 3G9 donor Vk.
CPVk46-14 was selected as the acceptor framework.

The chimpanzee JK gene segment of CPVk46-14 was
20 identical to that of CPVk46-1 (SEQ ID NO: 97) and was
selected as acceptor framework IV. The sequences of the
donor Vk3G9 and acceptor CPVk46-14 V regions were aligned and
the positions of their respective framework and CDRs were
determined as shown in Fig. 5.

25 The CDR residues were identified as defined by the
convention of Kabat et al., *supra*. The results show that
Vk3G9 and CPVk46-14 share 65% overall sequence identity, with
the framework regions I through III sharing 73% sequence
identity.

30 Framework residues that could influence CDR presentation
were identified by analysis of three-dimensional models based
on known antibody crystal structures. The residues of this
CDR-contacting set were compared among the aligned Vk3G9 and
CPVk46-14 sequences, and the positions of this set that
35 differed between Vk3G9 and the CPVk46-3 were marked. The CDRs
and marked residues of Vk3G9 (the donor antibody) were

transferred replacing the corresponding residues of CPV46-14 (the acceptor antibody). Lastly, the framework IV sequences of CPV46-14 replaced the corresponding framework IV residues of the 3G9 light chain variable region. The completed engineered 3G9 light chain V region is shown in SEQ ID NO: 77. Three donor framework residues were retained in the engineered light chain variable region at positions 3, 46 and 60.

The 3G9 heavy chain was engineered in analogous fashion. The amino acid sequence of donor antibody VH3G9 (SEQ ID NO: 75) was compared to each of the 9 chimpanzee VH sequences described above by computer homology searching. Clone CPVH41-18 (SEQ ID NO: 17) was identified as the chimpanzee VH region with the highest overall sequence similarity (53%) to the 3G9 donor VH.

The chimpanzee JH gene segment of CPVH41-18 was identical to CPVH41-9 (SEQ ID NO: 81) and was selected as acceptor framework IV. The sequences of the donor VH3G9 and chimpanzee acceptor V regions were aligned and the positions of their respective framework and CDRs determined as shown in Fig. 6.

The CDR residues were identified as defined by the convention of Kabat et al., *supra*. The results show that VH3G9 and CPVH41-18 share 53% overall sequence identity, with the framework regions I through III sharing 62% sequence identity.

Framework residues that could influence CDR presentation were identified by analysis of three-dimensional models based on known antibody crystal structures. The residues of this CDR-contacting set were compared among the aligned VH3G9 and CPVH41-18 sequences, and the twelve residues of the set that differed between VH3G9 and the chimpanzee acceptor frameworks were marked. The CDRs and the marked framework residues of donor antibody VH3G9 were transferred replacing the corresponding residues of CPVH41-18 (the acceptor antibody). Lastly, the framework IV sequences of CPVH41-18 replaced the corresponding framework IV residues of the 3G9 heavy chain variable region. The completed engineered 3G9 heavy chain V region is shown in SEQ ID NO: 78. Twelve donor framework residues were retained in the engineered heavy chain variable

region at positions 24, 27, 30, 38, 48, 66-69, 71, 73, and 94.

Example 9

5 Expression and Characterization of Engineered anti-
 Erythropoietin Receptor Monoclonal Antibodies

 The engineered 3G9 antibody was expressed in cells using methods well known to those skilled in the art. Briefly, genes encoding the complete engineered 3G9 VH and VK regions
10 were assembled from long synthetic oligonucleotides and ligated into appropriate eukaryotic expression vectors containing IgG1,K antibody constant regions. The expression vector contained a selectable marker for neomycin resistance and CMV promoter regulatory sequences. Subsequent
15 transfection of COS host cells resulted in the expression of engineered 3G9 (CP3G9).

 Culture supernatants from COS cells transiently transfected with chimpanzee framework engineered 3G9 were compared with another 3G9 variant for the ability to bind
20 human EPOR. The entire extracellular domain of the EPOR was expressed as recombinant protein, purified, and adsorbed onto the wells of ELISA plates. Dilutions of different antibodies were then tested for the ability to specifically bind to the solid phase associated EPOR.

25 HZ3G9 is a humanized variant of 3G9 in which human frameworks were used in traditional CDR grafting experiments. The humanized 3G9 heavy chain amino acid sequence is shown in SEQ ID NO: 79. The humanized 3G9 light chain sequence is shown in SEQ ID NO: 80. Previous experiments showed that
30 HZ3G9 retained the full binding affinity and avidity of the parental murine 3G9. Accordingly, since HZ3G9G1 is identical to the chimpanzee version in all respects except the V region cassette, it was used in the present comparative binding experiments as a surrogate for murine 3G9. Negative control
35 antibodies were also tested, including HZD12 which is a humanized antibody specific for human integrin, and CPB9 which is a chimpanzee framework engineered antibody specific for human integrins described above. Different concentrations of the 3G9 variants and control antibodies
40 were incubated for one hour. After washing, the bound

antibodies were detected by incubation with anti-human H+L antibody-enzyme conjugate, a final wash, and addition of chromagen.

The binding curves obtained for CP3G9 and HZ3G9 were superimposable. This result indicates that the human and the chimpanzee framework engineered versions of 3G9 have identical overall binding avidity for the specific antigen human EPOR. Since the constant regions of HZ3G9 and CP3G9 are identical, the results also suggest the full binding affinity of the original rodent 3G9 is retained in the chimpanzee version of 3G9. Accordingly, the results show that CDR grafting of rodent CDRs onto chimpanzee acceptor frameworks as described in the present invention retained the full binding avidity of the parental rodent antibody.

A BIAcore analysis (Pharmacia) was performed to determine the binding affinity for human EPOR of murine 3G9 and CP3G9. The interaction of CP3G9 as well as murine 3G9 with EPOR was characterized using a BIAcore 1000 biosensor. Descriptions of the instrumentation and the sensor surfaces are described in Brigham-Burke et al., *Anal. Biochem.*, 205:125-131 (1992).

CP3G9 was captured onto a sensor surface of immobilized protein A. The kinetic binding constants were determined by passing solutions of monomeric EPOR over the surface and monitoring binding versus time. The equilibrium dissociation constant for the interaction was then derived from the ratio of the kinetic constants. The parent murine 3G9 was captured onto a surface of protein A captured rabbit anti-mouse Fc specific polyclonal antibody. The kinetics and dissociation constant for the interaction with EPOR was determined as described above. All measurements were made in 10 mM sodium phosphate, 150 mM NaCl pH 7.2 3 mM EDTA and 0.005% Tween 20. The flow rate was 60 uL/min. The temperature was 20° C.

	$k_{\text{ass}} \text{ (M}^{-1}\text{s}^{-1}\text{)}$	$k_{\text{diss}} \text{ (s}^{-1}\text{)}$	$K_D \text{ (nM)}$
murine 3G9	1.2×10^6	4.0×10^{-3}	3.3
CP3G9	1.0×10^6	9.1×10^{-3}	9.1

These results show that the dissociation equilibrium constants determined for the murine and chimpanzee framework versions of 3G9 are within three fold of each other. This

data is in good agreement with the results of the ELISA-based study described above. Accordingly, the results show that the process used in generating the chimpanzee version of 3G9 largely retained the binding affinity of the original rodent mAb.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof, and, accordingly, reference should be made to the appended claims, rather than to the foregoing specification, as indicating the scope of the invention.

Claims

1. An antibody comprising donor CDRs derived from an antigen-specific donor antibody of a non-human species and acceptor framework residues derived from a non-human primate.

2. The antibody of claim 1 wherein the non-human primate is an Old World ape.

3. The antibody of claim 2 wherein the Old World ape is *Pan troglodytes*, *Pan paniscus* or *Gorilla gorilla*.

4. The antibody of claim 3 wherein the Old World ape is *Pan troglodytes*.

5. The antibody of claim 1 further comprising one or more CDR-contacting residues of the donor antibody.

6. The antibody of claim 1 comprising human or Old World ape constant regions.

7. The antibody of claim 1 wherein one or more solvent-exposed framework residues are replaced with corresponding residues from a homologous selected non-human primate framework.

8. The antibody of claim 1 wherein the non-human primate is an Old World monkey.

9. The antibody of claim 8 wherein the Old World monkey genus is *Macaca*.

10. The antibody of claim 9 wherein the Old World monkey is *Macaca cynomolgus*.

11. The antibody of claim 8 further comprising one or more CDR-contacting residues of the donor antibody.

12. The antibody of claim 8 comprising human or Old World ape constant regions.

13. The antibody of claim 8 wherein one or more solvent-exposed framework residues are replaced with corresponding residues from a homologous selected non-human primate framework.

14. A method for making an antibody having reduced immunogenicity in humans comprising grafting CDRs from antigen-specific non-human antibodies onto homologous Old World ape acceptor frameworks.

15. The method of claim 14 wherein the Old World ape acceptor framework is from *Pan troglodytes*, *Pan paniscus* or *Gorilla gorilla*.

16. The method of claim 15 wherein the Old World ape acceptor framework is from *Pan troglodytes*.

17. A method for making an antibody having reduced immunogenicity in humans comprising grafting CDRs from antigen-specific non-human antibodies onto homologous Old World monkey acceptor frameworks.

18. The method of claim 17 wherein the Old World monkey acceptor framework is from the genus *Macaca*.

19. The method of claim 18 wherein the Old World Monkey acceptor framework is from *Macaca cynomolgus*.

20. A chimpanzee VH acceptor framework I, II and III comprising an amino acid sequence as set forth in SEQ ID NOs: 10, 11, 12, 13, 14, 15, 16, 17 or 18.

21. A chimpanzee VH acceptor framework IV comprising an amino acid sequence as set forth in SEQ ID NOs: 81, 82, 83, 84 or 85.

22. A chimpanzee VK acceptor framework I, II and III comprising an amino acid sequence as set forth in SEQ ID NOs: 28, 29, 30, 31, 32, 33, 34, 35 or 36.

23. A chimpanzee VK acceptor framework IV comprising an amino acid sequence as set forth in SEQ ID NOs: 86 or 87.

24. A cynomolgus VH acceptor framework I, II and III comprising an amino acid sequence as set forth in SEQ ID NOs: 45, 46, 47, 48, 49, 50, 51 or 52.

25. A cynomolgus VH acceptor framework IV comprising an amino acid sequence as set forth in SEQ ID NOs: 88, 89, 90, 91, 92 or 93.

26. A cynomolgus VK acceptor framework I, II and III comprising an amino acid sequence as set forth in SEQ ID NOs: 59, 60, 61, 62, 63 or 64.

27. A cynomolgus VK acceptor framework IV comprising an amino acid sequence as set forth in SEQ ID NOs: 94, 95 or 96.

28. An isolated nucleic acid molecule encoding the amino acid sequence of SEQ ID NOs: 10, 11, 12, 13, 14, 15, 16, 17, 18, 28, 29, 30, 31, 32, 33, 34, 35 or 36.

29. An isolated nucleic acid molecule encoding the amino acid sequence of SEQ ID NOs: 81, 82, 83, 84, 85, 86 or 87.

30. An isolated nucleic acid molecule encoding the amino acid sequence of SEQ ID NOs: 45, 46, 47, 48, 49, 50, 51, 52, 59, 60, 61, 62, 63 or 64.

31. An isolated nucleic acid molecule encoding the amino acid sequence of SEQ ID NOs: 88, 89, 90, 91, 92, 93, 94, 95 or 96.

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Figure 1

4A6 DTVLTQSPA. LAVPPGERVT VSC**RASESVS** **TFLHWYQQKP** GHQP
C108G AVHMTQSPSS LSASVGDSVT ITC**RASQTIN** **IYLNWYQQKP** GKAP

*

*

4A6 KLLIY**LASKL** **ESGV**PARFSG GSGTDFTLT IDPVEADDTA TY**YCQQTW**ND
C108G KLLIF**DASIL** **QSGV**PSRFSG SSGTDFSLT IRS**LQPEDFA** TY**YCQCGW**GTH

4A6 **PRTF**GGGT KLELKR

C108G **PYNF**GQGT KLEIKR

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Figure 2

* * *

4A6 EVQLQQSGPE VGRPGSSVKI SCKASGYTFT ~~DYVLMNVK~~¹¹ QSPGQGLEWI
C108G EVQLVESGGG VVQPGGSLRL SCAASGFTFD ~~DFAMHWVR~~ QAPGKGLEWI

* * * * *

4A6 ~~GWIDPDYG~~ ~~TTDYAEKFKK~~ KATLTADTSS STAYIQLSSL TSEDATYFC
C108G ~~SLVSWDSY~~ ~~NIYHADSVKG~~ RFTISRDNRS NSLYLQMNDL RPEDTAIYFC

*

4A6 ARSRNYGG... ..YI NYWGQGVMTVS
C108G AKADTGGDFD YVSDSWRCAL DYWGQGTLLVTVS

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Figure 3

	1	CDR1	
VLB9	DIQMTQTTSS LSASLGDRVT ITCRSSQ.....DISNFLN	WYQQKPDGTV	
Cmp46-3	DIQMTQSPSS LSASVGDRVT ITCRASQ.....GISNYLA	WYQQKPGKAP	
	45	CDR2	CDR3 94
VLB9	KLLIYYTSTL HSGVPSRFSG SSGSTDYSLT ISNLEQEDIA TYFCQQGNTL		
Cmp46-3	KLLIYYASRL ESGVPSRFSG SSGSTDYTLT ISSLPEDFA TYTCQQYNSN		
	95		
VLB9	P..WTFGGGT NLEIKR		
cmp46-1	FGGGT KVEIKR		

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Figure 4

	1	11	21	CDR1	39	48
			* *		*	*
VHB9	QVQLQQSGAE	LMKPGASVKI	SCKATGYTFS	SYWIE..	WVK	QRPGHGLEWI
AMP41CL18	QVQLVQSGAE	VKKPGSSVKV	SCKVSGGTFS	TYGFS..	WVR	QAPGQGLEWM
	49	CDR2	66	76	83	92
			* * *			
VHB9	GEILP..RSG	NTNYNEKFKG	KATFTAETSS	NTAYMQLSSL	TPEDSAVYYC	
AMP41CL18	GMIIP..IVG	TVKYAQRFAQ	RVSINADTST	NIAYMELTSL		
RSEDTAVYYC						
	93	CDR3	104			
		**				
VHB9	SSRGVRGSM.....	DIW	GQGTSVTVSS			
AMP41CL18	ATDLTVTTNDAF.....	DI				
AMP41CL10			W GQGTSLTVSS			

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Figure 5

	1		CDR1	
		*		
VL3G9		DIVMTQSQKF	MSTSVGDRVS	VTCKASQ.....NVGTNVA WYQKPGQSP
VK46-14		DIQMTQSPSS	LSASVGDRVT	ITCRASQ.....SISNYLS WYQKPGKAP
	45		CDR2	CDR3 94
		*		*
VL3G9		KALIYSASYR	YSGVPDRFTG	SGSGTDFTLT ISNVQSEDLA EYFCQQYNSY
VK46-14		KLLIYYASTL	QSGVPSRFSG	SGSGTDFTLT ISSLPEDFA TYQCQHYGT
	95			
VL3G9		P...LTFGAGT	KLELK	
VK46-14		H...PTFGGGT	KVEIK	

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Figure 6

	1	11	21		CDR1	39	48
				* * *		*	*
VH3G9	QVQLQQPGAE	LVKSGASVKL	SCKASGSTFT	SYWQH	..WVK	QRPGRGLEWI	
Chimp41-18	QVQLVQSGAE	VKKPGSSVKV	SCKVSGGTFS	TYGFS	..WVR	QAPGQGLEWM	
	49	CDR2	66		76	83	92
				**** * *			
VH3G9	GRIDP	..NSG	GTKDNEKFKS	KATLTVDKPS	STAYMQLSSL	TSEDSAVYYC	
Chimp41-18	GMIIP	..IVG	TVKYAQRFG	RVSINADTST	NIAYMELTSL	RSEDTAVYYC	
	93	CDR3	104				
		*					
VH3G9	ARETYDSS	FAYW	GQGT	LVTVS		
Chimp41-18	ATDLTVTTN	DAFDIW	GQGT	MTVTVS		

SEQUENCE LISTING

<110> Taylor, Alexander H

<120> Monoclonal Antibodies with Reduced
Immunogenicity

<130> P50770

<150> 60/083,367

<151> 1998-04-28

<160> 97

<170> FastSEQ for Windows Version 3.0

<210> 1

<211> 429

<212> DNA

<213> Pan troglodytes

<220>

<221> CDS

<222> (1)...(429)

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atg aaa cac ctg tgg ttc ttc ctc ctg ctg gtg gca gct ccc aga tgg 48

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp

1 5 10 15

gtc ctg tcc cag gtg cag ttg cag gag tcg ggc cca gga ctg gtg aag 96

Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys

20 25 30

cct tca cag acc ttg tcc ctg acc tgc gct gtg tct ggt ggc tcc atc 144

Pro Ser Gln Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile

35	40	45	
act agt gct tac tac tat tgg agc tgg atc cgc cag tca cca ggg aag			192
Thr Ser Ala Tyr Tyr Tyr Trp Ser Trp Ile Arg Gln Ser Pro Gly Lys			
50	55	60	
gga ctg gag tgg att ggg agt atc tat tat agt ggg acc att ttc tcc			240
Gly Leu Glu Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Thr Ile Phe Ser			
65	70	75	80
aac cca tcc ctc aag agt cga gtc gcc atg tca gta ggc acg tcc aag			288
Asn Pro Ser Leu Lys Ser Arg Val Ala Met Ser Val Gly Thr Ser Lys			
85	90	95	
acc cag ttc tcc ctg agc ttg agt tct gtg acc gcc gcg gac acg gcc			336
Thr Gln Phe Ser Leu Ser Leu Ser Ser Val Thr Ala Ala Asp Thr Ala			
100	105	110	
gtg tac tac tgt gcg aga ggt ctg ctc ctc acc att gga ctg acc aac			384
Val Tyr Tyr Cys Ala Arg Gly Leu Leu Leu Thr Ile Gly Leu Thr Asn			
115	120	125	
tac tac ttt gac tac tgg ggc ccg gga acc ctg gtc acc gtc ttc			429
Tyr Tyr Phe Asp Tyr Trp Gly Pro Gly Thr Leu Val Thr Val Phe			
130	135	140	

<210> 2

<211> 414

<212> DNA

<213> Pan troglodytes

<220>

<221> CDS

<222> (1) ... (414)

<400> 2

atg aaa cac ctg tgg ttc ttc ctc ctg ctg gtg gca gct ccc aga tgg	48
Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp	
1 5 10 15	
gtc ctg tcc cag gtg cag cta cag gag tgc ggc cca gga cta gtg aag	96
Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys	
20 25 30	
ccg tca cag acc ctg tcc ctc acc tgc ggt gtc tct ggt gcc tcc atc	144
Pro Ser Gln Thr Leu Ser Leu Thr Cys Gly Val Ser Gly Ala Ser Ile	
35 40 45	
aat agt ggt gtt cat tac tgg gcc tgg ata cgc cag cct gca gga aag	192
Asn Ser Gly Val His Tyr Trp Ala Trp Ile Arg Gln Pro Ala Gly Lys	
50 55 60	
gga ctg gag tgg att ggc aat atc tat cat agt ggg agc gcc tac tac	240
Gly Leu Glu Trp Ile Gly Asn Ile Tyr His Ser Gly Ser Ala Tyr Tyr	
65 70 75 80	
act cca tcc ctc gag agt cga gtc tcc atg tca ata gag acg tcc aag	288
Thr Pro Ser Leu Glu Ser Arg Val Ser Met Ser Ile Glu Thr Ser Lys	
85 90 95	
agc cag ttc ttc cta aac tta aat tct ctg acc gcc gcg gac acg gct	336
Ser Gln Phe Phe Leu Asn Leu Asn Ser Leu Thr Ala Ala Asp Thr Ala	
100 105 110	
atc tat tat tgt gcg aga cga cat act tgc tca gac tac ttt gac ttt	384
Ile Tyr Tyr Cys Ala Arg Arg His Thr Ser Ser Asp Tyr Phe Asp Phe	
115 120 125	
tgg ggc cgc gga atc ctg gtc atc gtc tcc	414
Trp Gly Arg Gly Ile Leu Val Ile Val Ser	
130 135	

<210> 3

<211> 427

<212> DNA

<213> Pan troglodytes

<220>

<221> CDS

<222> (1) . . . (427)

<400> 3

atg ggg tca acc gcc atc ctc gcc ctc ctc ctg gct gtt ctc gaa gga 48
Met Gly Ser Thr Ala Ile Leu Ala Leu Leu Leu Ala Val Leu Glu Gly
1 5 10 15

gtc cgt gca gac gtg cag ctg gtg cag tcc gga gca gag gtg aaa aag 96
Val Arg Ala Asp Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20 25 30

ccc ggg gag tct ctg aag atc tcc tgt aag gtc tct gga aat gaa ttt 144
Pro Gly Glu Ser Leu Lys Ile Ser Cys Lys Val Ser Gly Asn Glu Phe
35 40 45

acc aac tac tgg atc gcc tgg gtg cgc cag atg tcc ggg aaa ggc ctg 192
Thr Asn Tyr Trp Ile Ala Trp Val Arg Gln Met Ser Gly Lys Gly Leu
50 55 60

gag tgg atg ggg agc atc tat cct ggt gac tct gat acc aga tac aac 240
Glu Trp Met Gly Ser Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Asn
65 70 75 80

ccg tcc ttc caa ggc caa gtc acc ttt tca gcc gac aag tcc atc acc 288
Pro Ser Phe Gln Gly Gln Val Thr Phe Ser Ala Asp Lys Ser Ile Thr
85 90 95

acc gcc tat ttg cag tgg agt agt ctg gag gcc tcg gac acc gcc atg 336
Thr Ala Tyr Leu Gln Trp Ser Ser Leu Glu Ala Ser Asp Thr Ala Met
100 105 110

tac tac tgt gcg agc cga aat cac ttt gtt ttc ggg gaa gtt att act 384
 Tyr Tyr Cys Ala Ser Arg Asn His Phe Val Phe Gly Glu Val Ile Thr
 115 120 125

act ttg acg gct ggg gcc agg gaa acc ctg ggt cac cgt ctc c 427
 Thr Leu Thr Ala Gly Ala Arg Glu Thr Leu Gly His Arg Leu
 130 135 140

<210> 4

<211> 402

<212> DNA

<213> Pan troglodytes

<220>

<221> CDS

<222> (1)...(402)

<400> 4

ttg ggg ctc cgc tgg gtt ttc ctt gtt gct ttt tta gaa ggt gtc cag 48
 Leu Gly Leu Arg Trp Val Phe Leu Val Ala Phe Leu Glu Gly Val Gln
 1 5 10 15

tgt gag gta cag ctg gtg gag tct ggg gga ggc ttg gta cag cct ggg 96
 Cys Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
 20 25 30

ggg tcc ttg aca ctc tcc tgt gca gcc tct gga ttc acc ttc agt agg 144
 Gly Ser Leu Thr Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg
 35 40 45

agt ggc atg cac tgg gtc cgc cag gct cca ggg aag gga ctg ggg tgg 192
 Ser Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Gly Trp
 50 55 60

ctt gca tac att gat tat ggc agt att ttc ata tac tac tcg gac tca 240
 Leu Ala Tyr Ile Asp Tyr Gly Ser Ile Phe Ile Tyr Tyr Ser Asp Ser

65	70	75	80	
gtg aag ggc cgc ttc acc atc tcc aga gac aac gcc aag aat tca ctc				288
Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu				
	85	90	95	
tat ctg caa atg aac agc ctg aga gcc gac gac acg gct ttt tat tac				336
Tyr Leu Gln Met Asn Ser Leu Arg Ala Asp Asp Thr Ala Phe Tyr Tyr				
	100	105	110	
tgt acg acc cat aat tgg ggg gag tta act gac tac tgg ggc cag gga				384
Cys Thr Thr His Asn Trp Gly Glu Leu Thr Asp Tyr Trp Gly Gln Gly				
	115	120	125	
acc ctg gtc acc gtc tcc				402
Thr Leu Val Thr Val Ser				
	130			

<210> 5

<211> 408

<212> DNA

<213> Pan troglodytes

<220>

<221> CDS

<222> (1)...(408)

<400> 5

atg gaa ttg ggg ctc cgc tgg gtt ttc ctt gtt gct ttt tta gaa ggt				48
Met Glu Leu Gly Leu Arg Trp Val Phe Leu Val Ala Phe Leu Glu Gly				
1	5	10	15	
gtc cag tgt gag gta cag ctg gtg gag tct ggg gga ggc ttg gta cag				96
Val Gln Cys Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln				
	20	25	30	

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cct ggg ggg tcc ttg aca ctc tcc tgt gca gcc tct gga ttc acc ttc      144
Pro Gly Gly Ser Leu Thr Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
      35              40              45

agt agg agt ggc atg cac tgg gtc cgc cag gct cca ggg aag gga ctg      192
Ser Arg Ser Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
      50              55              60

gag tgg ctt gca tac att gat tat ggc agt att ttc ata tac tac tcg      240
Glu Trp Leu Ala Tyr Ile Asp Tyr Gly Ser Ile Phe Ile Tyr Tyr Ser
      65              70              75              80

gac tca gtg aag ggc cgc ttc acc atc tcc aga gac aac gcc aag aat      288
Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
      85              90              95

tca ctc tat ctg caa atg aac agc ctg aga gcc gac gac acg gct ttt      336
Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Asp Asp Thr Ala Phe
      100             105             110

tat tac tgt acg acc cat aat tgg ggg gag tta act gac tac tgg ggc      384
Tyr Tyr Cys Thr Thr His Asn Trp Gly Glu Leu Thr Asp Tyr Trp Gly
      115             120             125

cag gga acc ctg gtc acc gtc tcc      408
Gln Gly Thr Leu Val Thr Val Ser
      130             135

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<210> 6

<211> 421

<212> DNA

<213> Pan troglodytes

<220>

<221> CDS

<222> (1) ... (421)

<400> 6

atg atg ggg tca acc gcc atc ctc gcc ctc ctc ctg gct gtt ctc caa 48

Met Met Gly Ser Thr Ala Ile Leu Ala Leu Leu Leu Ala Val Leu Gln

1 5 10 15

gga gtc tgt gca gag gtg cag ctg gtg cag tct gga gca gag gtg aaa 96

Gly Val Cys Ala Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys

20 25 30

aag ccc ggg gag tct ctg aag atc tcc tgt aag ggc tct gga tac agt 144

Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser

35 40 45

ttt acc aac tac tgg atg ggc tgg gtg tgc cag atg ccc ggg aaa ggc 192

Phe Thr Asn Tyr Trp Met Gly Trp Val Cys Gln Met Pro Gly Lys Gly

50 55 60

ccg gag tgc atg ggg atc atc tat cct gat gac tct gat acc aga tac 240

Pro Glu Cys Met Gly Ile Ile Tyr Pro Asp Asp Ser Asp Thr Arg Tyr

65 70 75 80

agc ccg tcc ttc caa ggc cag gtc acc atc tca gcc gac aag tcc atc 288

Ser Pro Ser Phe Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile

85 90 95

agc acc gcc tac cta caa tgg agc aac ctg aag gcc tcg gac acc gcc 336

Ser Thr Ala Tyr Leu Gln Trp Ser Asn Leu Lys Ala Ser Asp Thr Ala

100 105 110

ata tat tac tgt gcg aga tgt tat ggt tgg act act tgc gaa gct ttt 384

Ile Tyr Tyr Cys Ala Arg Cys Tyr Gly Trp Thr Thr Cys Glu Ala Phe

115 120 125

gat atc tgg ggc caa ggg aca atg gtc acc gtc tct t 421

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser

130 135 140

<210> 7
 <211> 417
 <212> DNA
 <213> Pan troglodytes

<220>
 <221> CDS
 <222> (1)...(417)

<400> 7

ttg tgg ttc ttc ctt ctc ctg gtg gca gct ccc aga tgg gtc ctg tcc	48
Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp Val Leu Ser	
1 5 10 15	
cag ctg cag ctg cag gag tcg ggc cca gga ctg gtg aag cct tca cag	96
Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln	
20 25 30	
acc ctg tcc ctc acc tgc act gtc tct ggt ggc tcc atc agc agt ggt	144
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly	
35 40 45	
agt tac tac tgg agt tgg atc cgg cag ccc gcc ggg aag cga ctg gag	192
Ser Tyr Tyr Trp Ser Trp Ile Arg Gln Pro Ala Gly Lys Arg Leu Glu	
50 55 60	
tgg att ggg tat att tat tat agt ggg agt acc tac tac aac cca tcc	240
Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser	
65 70 75 80	
ctc aag agt cga gtc acc ata tca gta gac acg tcc aag aac cag ttc	288
Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe	
85 90 95	
tcc ctg aag ctg agc tct gtg acc gcc gca gac acg gcc gtc tat tac	336

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
 100 105 110

tgt gcg aga tct ccc caa aac gta tta caa tct ttg gac tgc ttc gac 384
 Cys Ala Arg Ser Pro Gln Asn Val Leu Gln Ser Leu Asp Cys Phe Asp
 115 120 125

ccc tgg ggc cag gga acc ctg gtc acc gtc tcc 417
 Pro Trp Gly Gln Gly Thr Leu Val Thr Val Ser
 130 135

<210> 8
 <211> 369
 <212> DNA
 <213> Pan troglodytes

<220>
 <221> CDS
 <222> (1)...(369)

<400> 8

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 Val Gln Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
 1 5 10 15

cct ggg tcc tca gtg aag gtc tcc tgc aag gtt tcc gga ggc acc ttc 96
 Pro Gly Ser Ser Val Lys Val Ser Cys Lys Val Ser Gly Gly Thr Phe
 20 25 30

agc acc tat ggt ttc agc tgg gtg cgg cag gcc cct gga caa ggg ctt 144
 Ser Thr Tyr Gly Phe Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
 35 40 45

gag tgg atg gga atg atc atc cct atc gtt ggc aca gta aag tac gca 192
 Glu Trp Met Gly Met Ile Ile Pro Ile Val Gly Thr Val Lys Tyr Ala
 50 55 60

cag agg ttc cag ggc aga gtc tca att aat gcg gac aca tcc acg aat 240
 Gln Arg Phe Gln Gly Arg Val Ser Ile Asn Ala Asp Thr Ser Thr Asn
 65 70 75 80

ata gcc tac atg gag ctg acc agc ctg aga tct gag gac acg gcc gtc 288
 Ile Ala Tyr Met Glu Leu Thr Ser Leu Arg Ser Glu Asp Thr Ala Val
 85 90 95

tat tac tgt gcg aca gat ctg acg gtg act act aat gat gca ttt gat 336
 Tyr Tyr Cys Ala Thr Asp Leu Thr Val Thr Thr Asn Asp Ala Phe Asp
 100 105 110

atc tgg ggc caa ggg aca atg gtc acc gtc tct 369
 Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser
 115 120

<210> 9

<211> 423

<212> DNA

<213> Pan troglodytes

<220>

<221> CDS

<222> (1)...(423)

<400> 9

atg gag ttt ggg ctg agc tgg ctt ttt ctt gtg gct att tta aaa ggt 48
 Met Glu Phe Gly Leu Ser Trp Leu Phe Leu Val Ala Ile Leu Lys Gly
 1 5 10 15

gtc cag tgt gag gtg cag ctg gtg gag tct ggg gaa ggc ttg gta aag 96
 Val Gln Cys Glu Val Gln Leu Val Glu Ser Gly Glu Gly Leu Val Lys
 20 25 30

cct ggg ggt tcc ctg aga ctc tcg tgt gca gcc tct gga ttc acc ttc 144

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45

agt agt ttt ctt atg ttc tgg gtc cgc cag gct cca gaa aag ggg ctg 192
Ser Ser Phe Leu Met Phe Trp Val Arg Gln Ala Pro Glu Lys Gly Leu
50 55 60

gag tgg gtc tca act att gat gtt agt ggt ggt aat atg tgg tac cga 240
Glu Trp Val Ser Thr Ile Asp Val Ser Gly Gly Asn Met Trp Tyr Arg
65 70 75 80

gac tct gtc aag ggc cga ttc acc atg tcc aga gac aat tcc aag aac 288
Asp Ser Val Lys Gly Arg Phe Thr Met Ser Arg Asp Asn Ser Lys Asn
85 90 95

aca ctg tat ctg caa atg acc agc ctg aga gcc gac gac acg gcc gtt 336
Thr Leu Tyr Leu Gln Met Thr Ser Leu Arg Ala Asp Asp Thr Ala Val
100 105 110

tac tat tgt gcg aga gag gga cga gac cct agc ggc act tgg gga tac 384
Tyr Tyr Cys Ala Arg Glu Gly Arg Asp Pro Ser Gly Thr Trp Gly Tyr
115 120 125

ttt gac tac tgg ggc cag gga atc ctg gtc acc gtc tcc 423
Phe Asp Tyr Trp Gly Gln Gly Ile Leu Val Thr Val Ser
130 135 140

<210> 10

<211> 97

<212> PRT

<213> Pan troglodytes

<220>

<221> DOMAIN

<222> (31)...(37)

<223> CDRI

<221> DOMAIN

<222> (52)...(67)

<223> CDRII

<400> 10

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
 1 5 10 15
 Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Thr Ser Ala
 20 25 30
 Tyr Tyr Tyr Trp Ser Trp Ile Arg Gln Ser Pro Gly Lys Gly Leu Glu
 35 40 45
 Trp Ile Gly Ser Ile Tyr Tyr Ser Gly Thr Ile Phe Ser Asn Pro Ser
 50 55 60
 Leu Lys Ser Arg Val Ala Met Ser Val Gly Thr Ser Lys Thr Gln Phe
 65 70 75 80
 Ser Leu Ser Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
 85 90 95
 Cys

<210> 11

<211> 96

<212> PRT

<213> Pan troglodytes

<220>

<221> DOMAIN

<222> (31)...(37)

<223> CDRI

<221> DOMAIN

<222> (52)...(67)

<223> CDRII

<400> 11

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln

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      1             5             10             15
Thr Leu Ser Leu Thr Cys Gly Val Ser Gly Ala Ser Ile Asn Ser Gly
      20             25             30
Val His Tyr Trp Ala Trp Ile Arg Gln Pro Ala Gly Lys Gly Leu Glu
      35             40             45
Trp Ile Gly Asn Ile Tyr His Ser Gly Ser Ala Tyr Tyr Thr Pro Ser
      50             55             60
Leu Glu Ser Arg Val Ser Met Ser Ile Glu Thr Ser Lys Ser Gln Phe
      65             70             75             80
Phe Leu Asn Leu Asn Ser Leu Thr Ala Asp Thr Ala Ile Tyr Tyr Cys
      85             90             95

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<210> 12
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<212> PRT
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<220>
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<223> CDRI

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<221> DOMAIN
<222> (50)...(66)
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<400> 12
Asp Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
      1             5             10             15
Ser Leu Lys Ile Ser Cys Lys Val Ser Gly Asn Glu Phe Thr Asn Tyr
      20             25             30
Trp Ile Ala Trp Val Arg Gln Met Ser Gly Lys Gly Leu Glu Trp Met
      35             40             45
Gly Ser Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Asn Pro Ser Phe
      50             55             60
Gln Gly Gln Val Thr Phe Ser Ala Asp Lys Ser Ile Thr Thr Ala Tyr
      65             70             75             80

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<210> 13
<211> 96
<212> PRT
<213> Pan troglodytes
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<220>  
<221> DOMAIN  
<222> (31) ... (35)  
<223> CDRI
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<221> DOMAIN
<222> (50) ... (66)
<223> CDRII
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Asp	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Glu
1				5					10					15	
Ser	Leu	Lys	Ile	Ser	Cys	Lys	Val	Ser	Gly	Asn	Glu	Phe	Thr	Asn	Tyr
			20					25					30		
Trp	Ile	Ala	Trp	Val	Arg	Gln	Met	Ser	Gly	Lys	Gly	Leu	Glu	Trp	Met
		35					40					45			
Gly	Ser	Ile	Tyr	Pro	Gly	Asp	Ser	Asp	Thr	Arg	Tyr	Asn	Pro	Ser	Phe
	50					55					60				
Gln	Gly	Gln	Val	Thr	Phe	Ser	Ala	Asp	Lys	Ser	Ile	Thr	Thr	Ala	Tyr
65					70					75					80
Leu	Gln	Trp	Ser	Ser	Leu	Glu	Ala	Ser	Asp	Thr	Ala	Met	Tyr	Tyr	Cys
				85					90					95	

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<210> 14
<211> 96
<212> PRT
<213> Pan troglodytes
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<220>

<221> DOMAIN

<222> (31)...(35)

<223> CDRI

<221> DOMAIN

<222> (50)...(66)

<223> CDRII

<400> 14

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Thr Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Arg Ser
 20 25 30
 Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Gly Trp Leu
 35 40 45
 Ala Tyr Ile Asp Tyr Gly Ser Ile Phe Ile Tyr Tyr Ser Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Asp Asp Thr Ala Phe Tyr Tyr Cys
 85 90 95

<210> 15

<211> 96

<212> PRT

<213> Pan troglodytes

<220>

<221> DOMAIN

<222> (31)...(35)

<223> CDRI

<221> DOMAIN

<222> (50)...(66)

<223> CDRII

<400> 15

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
 1 5 10 15
 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
 20 25 30
 Trp Met Gly Trp Val Cys Gln Met Pro Gly Lys Gly Pro Glu Cys Met
 35 40 45
 Gly Ile Ile Tyr Pro Asp Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
 50 55 60
 Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 Leu Gln Trp Ser Asn Leu Lys Ala Ser Asp Thr Ala Ile Tyr Tyr Cys
 85 90 95

<210> 16

<211> 97

<212> PRT

<213> Pan troglodytes

<220>

<221> DOMAIN

<222> (31)...(37)

<223> CDRI

<221> DOMAIN

<222> (52)...(67)

<223> CDRII

<400> 16

Gln Leu Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
 1 5 10 15
 Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
 20 25 30
 Ser Tyr Tyr Trp Ser Trp Ile Arg Gln Pro Ala Gly Lys Arg Leu Glu
 35 40 45
 Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
 50 55 60
 Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe

Cys

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<221> DOMAIN
<222> (50) ... (66)
<223> CDRII
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<210> 18
<211> 96
<212> PRT
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<213> Pan troglodytes

<220>

<221> DOMAIN

<222> (31)...(35)

<223> CDRI

<221> DOMAIN

<222> (50)...(66)

<223> CDRII

<400> 18

Glu	Val	Gln	Leu	Val	Glu	Ser	Gly	Glu	Gly	Leu	Val	Lys	Pro	Gly	Gly
1				5						10					15
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Phe
			20						25					30	
Leu	Met	Phe	Trp	Val	Arg	Gln	Ala	Pro	Glu	Lys	Gly	Leu	Glu	Trp	Val
		35					40						45		
Ser	Thr	Ile	Asp	Val	Ser	Gly	Gly	Asn	Met	Trp	Tyr	Arg	Asp	Ser	Val
		50				55						60			
Lys	Gly	Arg	Phe	Thr	Met	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
65					70					75				80	
Leu	Gln	Met	Thr	Ser	Leu	Arg	Ala	Asp	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
					85					90				95	

<210> 19

<211> 381

<212> DNA

<213> Pan troglodytes

<220>

<221> CDS

<222> (1)...(381)

<400> 19

atg	agg	gtc	cct	gct	cag	ctc	ctg	ggg	ctc	ctg	ctc	tgg	ctc	tca
Met	Arg	Val	Pro	Ala	Gln	Leu	Leu	Gly	Leu	Leu	Leu	Trp	Leu	Ser

48

1	5	10	15	
ggt gcc aga tgt gac atc cag atg acc cag ttt cca tcc tcc ctg tct				96
Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Phe Pro Ser Ser Leu Ser				
	20	25	30	
gca tct gta gga gac aga gtc acc atc act tgc cag tca agt cag agc				144
Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Gln Ser Ser Gln Ser				
	35	40	45	
att tac aac tgc ttg agt tgg tat cag cag aaa cca ggg aag gcc cct				192
Ile Tyr Asn Cys Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro				
	50	55	60	
aca ctc cta atc tat ggt gca ttc acc ttg aat agt ggg gtc cca tca				240
Thr Leu Leu Ile Tyr Gly Ala Phe Thr Leu Asn Ser Gly Val Pro Ser				
	65	70	75	80
aga ttc agt ggc agt gga tct ggc aca gat ttc act ctc acc atc agc				288
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser				
	85	90	95	
aat ctg caa cct gaa gat ttt gca aca tat tac tgt cag cgt ggt tac				336
Asn Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Arg Gly Tyr				
	100	105	110	
ggc aca cag ctc act ttc ggt gga ggg acc aag gtg gag atc aag				381
Gly Thr Gln Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys				
	115	120	125	

<210> 20

<211> 384

<212> DNA

<213> Pan troglodytes

<220>

<221> CDS

<222> (1)...(384)

<400> 20

atg gac atg agg gtc ccc gct cag ctc ctg ggg ctc ctg ctg ctc tgg 48
 Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
 1 5 10 15

ctc cca ggt acc aga tgt gac atc cag atg acc cag tct cca tcc tcc 96
 Leu Pro Gly Thr Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
 20 25 30

ctg tct gca tct gta gga gac aga gtc acc atc act tgc cgg gcc agt 144
 Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
 35 40 45

cag ggc att agc aat tat tta gcc tgg tat cag cag aaa cca ggg aaa 192
 Gln Gly Ile Ser Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
 50 55 60

gcc cct aag ctc ctc atc tat tat gca tcc aga ttg gaa agt ggg gtc 240
 Ala Pro Lys Leu Leu Ile Tyr Tyr Ala Ser Arg Leu Glu Ser Gly Val
 65 70 75 80

cca tca agg ttc agc ggc agt gga tct ggg acg gat tac act ctc acc 288
 Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr
 85 90 95

atc agc agc ctg cag cct gaa gat ttt gca act tat tac tgt caa cag 336
 Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
 100 105 110

tat aac agt aac ccc ttt tcg gtg gag gga cca agg tgg aga tca aac 384
 Tyr Asn Ser Asn Pro Phe Ser Val Glu Gly Pro Arg Trp Arg Ser Asn
 115 120 125

<210> 21

<211> 384

<212> DNA

<213> Pan troglodytes

<220>

<221> CDS

<222> (1)...(384)

<400> 21

atg tcg cca tca caa ctc att ggg ttt ctg ctg ctc tgg gtt cca gcc 48
 Met Ser Pro Ser Gln Leu Ile Gly Phe Leu Leu Leu Trp Val Pro Ala
 1 5 10 15

tcc agg ggt gaa att gtg ctg act cag tct cca gac ttt cag tct gtg 96
 Ser Arg Gly Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser Val
 20 25 30

cct cca aag gag aaa gtc acc atc acc tgc cgg gcc agt cag agc att 144
 Pro Pro Lys Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile
 35 40 45

ggc agt agc tta cac tgg tac cag cag aaa cca ggt cag tct cca aag 192
 Gly Ser Ser Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys
 50 55 60

ctc ctc atc aag tat gct tcc cag tcc atc tca ggg gtc ccc tcg agg 240
 Leu Leu Ile Lys Tyr Ala Ser Gln Ser Ile Ser Gly Val Pro Ser Arg
 65 70 75 80

ttc agt ggc agt gga tct ggg aca gat ttc acc ctc acc atc aat agc 288
 Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser
 85 90 95

ctg gaa gct gaa gat gct gca acg tat tac tgt cag caa agt agt aat 336
 Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Ser Ser Asn
 100 105 110

tta cct cat acg ctc act ttc ggt gga ggg acc aag gtg gag atc aaa 384
 Leu Pro His Thr Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys

115

120

125

<210> 22

<211> 372

<212> DNA

<213> Pan troglodytes

<220>

<221> CDS

<222> (1)...(372)

<400> 22

gtc cct gct cag ctc ctg ggg ctc ctg ctg ctc tgg ctc tca ggt gcc 48
 Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp Leu Ser Gly Ala

1

5

10

15

aga tgt gac atc cag atg acc cag tct cca tcc tcc ctg tct gca tct 96
 Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser

20

25

30

gta gga gac aga gtc acc atc act tgc cag gca agt cag agc att agc 144
 Val Gly Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Ser Ile Ser

35

40

45

aac tat ttg agt tgg tat cag cag aaa cca ggg aaa gcc cct aag ctc 192
 Asn Tyr Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu

50

55

60

ctg atc tat gat gca tcc act ttg caa agt ggg gtc cca tca agg ttc 240
 Leu Ile Tyr Asp Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe

65

70

75

80

agt ggc agt gga tct ggg aca gat ttc act ctc acc atc agc agt ctg 288

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu
 85 90 95

caa cct gaa gat ttt gca aca tat tac tgt cag cgt ggt tac ggt aca 336
 Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Arg Gly Tyr Gly Thr
 100 105 110

ctc act ttc ggt gga ggg acc aag gtg gag atc aaa 372
 Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 115 120

<210> 23

<211> 384

<212> DNA

<213> Pan troglodytes

<220>

<221> CDS

<222> (1)...(384)

<400> 23

atg gaa gcc cca gcg cag ctt ctc ttc ctc ctg cta ctc tgg ctc cca 48
 Met Glu Ala Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
 1 5 10 15

gat acc acc gga gaa ata gtg ttg acg cag tct cca gcc acc ctg tct 96
 Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser
 20 25 30

ttg tct cca ggg gaa aga gcc acc ctc tcc tgc agg gcc agt cag agt 144
 Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
 35 40 45

gtt agc agg tac tta gcc tgg tac cag cag aaa cct ggc cag gct ccc 192
 Val Ser Arg Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro
 50 55 60

agg ctc ctc atc tat ggt gca tcc aac agg gcc act ggc atc cca gcc 240
 Arg Leu Leu Ile Tyr Gly Ala Ser Asn Arg Ala Thr Glu Ile Pro Ala
 65 70 75 80

agg ttc agt ggc agt ggg tct agg aca gac ttc act ctc acc atc agc 288
 Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Ser
 85 90 95

agc gtg gag cct gaa gat ttt gca gtt tat tac tgt cag cag tat aat 336
 Ser Val Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn
 100 105 110

aac cag cct ctg atc gcc ttc ggc caa ggg aca cga ctg gag att aaa 384
 Asn Gln Pro Leu Ile Ala Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
 115 120 125

<210> 24

<211> 387

<212> DNA

<213> Pan troglodytes

<220>

<221> CDS

<222> (1)...(387)

<400> 24

atg gac atg agg gtc ccc gct cag ctc ctg ggg ctc ctg ctg ctc tgg 48
 Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
 1 5 10 15

ttc cca ggt gcc aaa tgt gac atc cag atg acc cag tct cct tcc acc 96
 Phe Pro Gly Ala Lys Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Thr
 20 25 30

ctg tct gcc tcc ata gga gac aga gtc acc atc act tgt cgg gct agt 144

25

Leu Ser Ala Ser Ile Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
 35 40 45
 cag ggc atc tat aat tat ttg aat tgg tat cag caa aaa cca ggg aga 192
 Gln Gly Ile Tyr Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Arg
 50 55 60
 gcc cct gga ctc ctc atc ttt ggt gcc agg aat ttg gag act ggg gtc 240
 Ala Pro Gly Leu Leu Ile Phe Gly Ala Arg Asn Leu Glu Thr Gly Val
 65 70 75 80
 cca tca aca ttc agc ggc agt ggt tcc ggg aca cac ttc act ctc acc 288
 Pro Ser Thr Phe Ser Gly Ser Gly Ser Gly Thr His Phe Thr Leu Thr
 85 90 95
 atc agc agc ctg cag cct ggt gat ttt gcg act tat tac tgt cag caa 336
 Ile Ser Ser Leu Gln Pro Gly Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
 100 105 110
 tat tat act acc ccg tat act ttt ggc cag ggg acc aag ctg gag atc 384
 Tyr Tyr Thr Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
 115 120 125
 aaa 387
 <210> 25
 <211> 387
 <212> DNA
 <213> Pan troglodytes
 <220>
 <221> CDS
 <222> (1)...(387)
 <400> 25
 atg gac atg agg gtc ccc gct cag ctc ctg ggg ctc ctg ctg ctc tgt 48
 Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Cys

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<210> 26
<211> 372
<212> DNA
<213> Pan troglodytes
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<222> (1) ... (372)

cga acg ttc ggc caa ggg acc aag ctg gaa atc aaa 372
Arg Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
115 120

<220>
<221> CDS
<222> (1) ... (387)

atg gac atg agg gtc ccc gct cag ctc ctg ggg ctc ctg ctg ctc tgg 48
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

ctc tca ggt acc aga tgt gac atc cag atg acc cag tct cca tcc tcc 96
Leu Ser Gly Thr Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

ctg tct gca tct gta gga gac aga gtc acc atc act tgc cgg gca agt 144
Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

cag agc att agc aac tat ttg agt tgg tat cag cag aaa cca ggg aaa 192
Gln Ser Ile Ser Asn Tyr Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

gcc cct aag ctc ctg atc tat tat gca tcc act ttg caa agt ggg gtc 240
Ala Pro Lys Leu Leu Ile Tyr Tyr Ala Ser Thr Leu Gln Ser Gly Val
65 70 75 80

cca tca agg ttc agt ggc agt gga tct ggg aca gat ttc act ctc acc 288
Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
85 90 95

atc agc agt ctg caa cct gaa gat ttt gca act tat tac tgt cag cat 336
Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His

100 105 110

ggt tac ggt aca cat ccc act ttc ggt gga ggg acc aag gtg gag atc 384

Gly Tyr Gly Thr His Pro Thr Phe Gly Gly Gly Thr Lys Val Glu Ile

115 120 125

aaa 387

<210> 28

<211> 88

<212> PRT

<213> Pan troglodytes

<220>

<221> DOMAIN

<222> (24)...(34)

<223> CDRI

<221> DOMAIN

<222> (50)...(66)

<223> CDRII

<400> 28

Asp Ile Gln Met Thr Gln Phe Pro Ser Ser Leu Ser Ala Ser Val Gly

1 5 10 15

Asp Arg Val Thr Ile Thr Cys Gln Ser Ser Gln Ser Ile Tyr Asn Cys

20 25 30

Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Thr Leu Leu Ile

35 40 45

Tyr Gly Ala Phe Thr Leu Asn Ser Gly Val Pro Ser Arg Phe Ser Gly

50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Leu Gln Pro

65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys

85

<210> 29

30

<211> 88
 <212> PRT
 <213> Pan troglodytes

<220>
 <221> DOMAIN
 <222> (24)...(34)
 <223> CDRI

<221> DOMAIN
 <222> (50)...(66)
 <223> CDRII

<400> 29

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1             5             10             15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr
             20             25             30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
             35             40             45
Tyr Tyr Ala Ser Arg Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
             50             55             60
Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65             70             75             80
Glu Asp Phe Ala Thr Tyr Tyr Cys
             85
  
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<210> 30
 <211> 88
 <212> PRT
 <213> Pan troglodytes

<220>
 <221> DOMAIN
 <222> (24)...(34)
 <223> CDRI

<223> CDR II

Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser Val Pro Pro Lys
 1 5 10 15
 Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Gly Ser Ser
 20 25 30
 Leu His Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
 35 40 45
 Lys Tyr Ala Ser Gln Ser Ile Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Glu Ala
 65 70 75 80
 Glu Asp Ala Ala Thr Tyr Tyr Cys
 85

<213> Pan troglodytes

<223> CDRI

<223> CDR II

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
  1             5             10             15
Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Ser Ile Ser Asn Tyr
      20             25             30
                        32

```

Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Asp Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Ala Thr Tyr Tyr Cys
 85

<210> 32

<211> 88

<212> PRT

<213> Pan troglodytes

<220>

<221> DOMAIN

<222> (24)...(34)

<223> CDRI

<221> DOMAIN

<222> (50)...(66)

<223> CDRII

<400> 32

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1 5 10 15
 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Arg Tyr
 20 25 30
 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
 35 40 45
 Tyr Gly Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Glu Pro
 65 70 75 80
 Glu Asp Phe Ala Val Tyr Tyr Cys
 85

<210> 33
 <211> 88
 <212> PRT
 <213> Pan troglodytes

<220>
 <221> DOMAIN
 <222> (24)...(34)
 <223> CDRI

<221> DOMAIN
 <222> (50)...(66)
 <223> CDRII

<400> 33

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Thr	Leu	Ser	Ala	Ser	Ile	Gly
1				5					10					15	
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Gly	Ile	Tyr	Asn	Tyr
				20				25						30	
Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Arg	Ala	Pro	Gly	Leu	Leu	Ile
				35				40					45		
Phe	Gly	Ala	Arg	Asn	Leu	Glu	Thr	Gly	Val	Pro	Ser	Thr	Phe	Ser	Gly
				50				55					60		
Ser	Gly	Ser	Gly	Thr	His	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
				65				70					75		80
Gly	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys								
								85							

<210> 34
 <211> 88
 <212> PRT
 <213> Pan troglodytes

<220>
 <221> DOMAIN
 <222> (24)...(34)
 <223> CDRI

<221> DOMAIN

<222> (50)...(66)

<223> CDRII

<400> 34

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15
 Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Leu Asp Ile Ser Thr Trp
 20 25 30
 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Pro Leu Ile
 35 40 45
 Tyr Ala Ala Ser Thr Leu Pro Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Ser Ala Thr Tyr Tyr Cys
 85

<210> 35

<211> 88

<212> PRT

<213> Pan troglodytes

<220>

<221> DOMAIN

<222> (24)...(34)

<223> CDRI

<221> DOMAIN

<222> (50)...(66)

<223> CDRII

<400> 35

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
 35

20 25 30
 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Asp Asp Phe Ala Thr Tyr Tyr Cys
 85

<210> 36
 <211> 88
 <212> PRT
 <213> Pan troglodytes

<220>
 <221> DOMAIN
 <222> (24)...(34)
 <223> CDRI

<221> DOMAIN
 <222> (50)...(66)
 <223> CDRII

<400> 36

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Asn Tyr
 20 25 30
 Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Tyr Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Ala Thr Tyr Tyr Cys
 85

<210> 37

<211> 408

<212> DNA

<213> Macaca cynomolgus

<220>

<221> CDS

<222> (1)...(408)

<400> 37

atg gag ttt gga ctg agc tgg gtt ttc ctt gtc gct att ttc aaa ggt 48
 Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Ile Phe Lys Gly
 1 5 10 15

gtc cag tgt gaa gtg cag ttg gtg gag tct ggg gga ggc ttg gta cag 96
 Val Gln Cys Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
 20 25 30

ccg ggg ggg tcc ctg aga ctc gcc tgt gta ggc tct gga ttc gcc ttc 144
 Pro Gly Gly Ser Leu Arg Leu Ala Cys Val Gly Ser Gly Phe Ala Phe
 35 40 45

aga aac acc agg atg cac tgg att cga cag act cca gga aag agg ctg 192
 Arg Asn Thr Arg Met His Trp Ile Arg Gln Thr Pro Gly Lys Arg Leu
 50 55 60

gag tgg gtg gcc gac ata aag ttt gat gga agt gat ttt tac tat gta 240
 Glu Trp Val Ala Asp Ile Lys Phe Asp Gly Ser Asp Phe Tyr Tyr Val
 65 70 75 80

gac tct gtg aag ggc cga ttc acc atc tcc aga gac aac gcc aag aac 288
 Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
 85 90 95

tcc ctc tat ctg gaa atg aac agc ctg aga cct gat gac aca gcc gtc 336
 Ser Leu Tyr Leu Glu Met Asn Ser Leu Arg Pro Asp Asp Thr Ala Val

37

100	105	110	
tat ttc tgt gtg aga gaa tac aga gat gga ctg gat gtc tgg ggc cgg			384
Tyr Phe Cys Val Arg Glu Tyr Arg Asp Gly Leu Asp Val Trp Gly Arg			
115	120	125	
gga gtt ctg gtc acc gtc tcc tca			408
Gly Val Leu Val Thr Val Ser Ser			
130	135		
<210> 38			
<211> 381			
<212> DNA			
<213> Macaca cynomolgus			
<220>			
<221> CDS			
<222> (1)...(381)			
<400> 38			
gtg aca gct ccc aga tgg gtc ctg tcc cag gtg caa ttg cag gag tcg			48
Val Thr Ala Pro Arg Trp Val Leu Ser Gln Val Gln Leu Gln Glu Ser			
1	5	10	15
ggc cca gga ctg gtg aag cct tcg gag acc ctg tcc ctc act tgt act			96
Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr			
20	25	30	
gtc tct ggt gac tcc atc acc act gtc ttc tgg agc tgg ctc cgc cag			144
Val Ser Gly Asp Ser Ile Thr Thr Val Phe Trp Ser Trp Leu Arg Gln			
35	40	45	
tcg cca ggg att ggg ctg gag tgg att ggg aat ttt gct ggt agt act			192
Ser Pro Gly Ile Gly Leu Glu Trp Ile Gly Asn Phe Ala Gly Ser Thr			
50	55	60	

ccg gaa acg aac tac aat ccc tcc ctc aag aat cga gcc acc att tca 240
 Pro Glu Thr Asn Tyr Asn Pro Ser Leu Lys Asn Arg Ala Thr Ile Ser
 65 70 75 80

aaa gac acg ccc acg aat caa ttt ttc ctg agg ctg acg tct gtg acc 288
 Lys Asp Thr Pro Thr Asn Gln Phe Phe Leu Arg Leu Thr Ser Val Thr
 85 90 95

gcc gcg gac acg gcc gtc tac ttc tgt gcg aga gga ggg gga gcc ggc 336
 Ala Ala Asp Thr Ala Val Tyr Phe Cys Ala Arg Gly Gly Gly Ala Gly
 100 105 110

aac cca ctc act tgg ggc cag gga gtc cag gtc acc gtc tcc tca 381
 Asn Pro Leu Thr Trp Gly Gln Gly Val Gln Val Thr Val Ser Ser
 115 120 125

<210> 39

<211> 417

<212> DNA

<213> Macaca cynomolgus

<220>

<221> CDS

<222> (1)...(417)

<400> 39

atg ggg tca act gcc atc ctc gcc ctc ctc ctg gct gtt ctc caa gga 48
 Met Gly Ser Thr Ala Ile Leu Ala Leu Leu Leu Ala Val Leu Gln Gly
 1 5 10 15

gtc tgt gcc gag gtg cat ctg gtg cag tct gga gca cag gtg aaa agg 96
 Val Cys Ala Glu Val His Leu Val Gln Ser Gly Ala Gln Val Lys Arg
 20 25 30

ccc ggg gaa tct ctg agg atc tcc tgt aag act tct gga tac acc ttt 144
 Pro Gly Glu Ser Leu Arg Ile Ser Cys Lys Thr Ser Gly Tyr Thr Phe

35	40	45	
acc gac agc tgg atc agc tgg gtg cgc cag atg ccc ggg aaa ggc ctg			192
Thr Asp Ser Trp Ile Ser Trp Val Arg Gln Met Pro Gly Lys Gly Leu			
50	55	60	
gag tgg atg gga aac atc tat cct ggt gat tct gat tcc aga tac aac			240
Glu Trp Met Gly Asn Ile Tyr Pro Gly Asp Ser Asp Ser Arg Tyr Asn			
65	70	75	80
ccg tcc ttc caa ggc cgc gtc act atc tca gtc gac aag tcc atc agt			288
Pro Ser Phe Gln Gly Arg Val Thr Ile Ser Val Asp Lys Ser Ile Ser			
85	90	95	
acc acc tac ctg cag tgg agc agc ctg aag gcc tcg gac act gcc aca			336
Thr Thr Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Thr			
100	105	110	
tat tac tgt gcg aag ata gat agc aac tac tac agc cgg ttc gaa gtc			384
Tyr Tyr Cys Ala Lys Ile Asp Ser Asn Tyr Tyr Ser Arg Phe Glu Val			
115	120	125	
tgg ggc ccc gga gtc atg gtc acc gtc tcc tca			417
Trp Gly Pro Gly Val Met Val Thr Val Ser Ser			
130	135		

<210> 40

<211> 423

<212> DNA

<213> Macaca cynomolgus

<220>

<221> CDS

<222> (1)...(423)

<400> 40

atg aag cac ctg tgg ttc ttc ctc ctc ctg gtg gca gct cct aga tgg	48
Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp	
1 5 10 15	
gtc ctg tcc cag gtg cag ttg cag gag tcg ggc cca gga gtg gtg aag	96
Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Val Val Lys	
20 25 30	
cct tcg gag acc ctg tcc ctc acc tgc act gtc tct ggt ggc tcc ttc	144
Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Phe	
35 40 45	
agt act tac tac tgg aat tgg atc cgc cag ccc cca ggg aag gga ctg	192
Ser Thr Tyr Tyr Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu	
50 55 60	
gag tgg att gga tat atc ggt ggt ggt ggt ggt cgc ccc aac tac aat	240
Glu Trp Ile Gly Tyr Ile Gly Gly Gly Gly Gly Arg Pro Asn Tyr Asn	
65 70 75 80	
tcc tcc ctc aag agt cgc atc acc ctg tca cta gac gcg tcc aag aac	288
Ser Ser Leu Lys Ser Arg Ile Thr Leu Ser Leu Asp Ala Ser Lys Asn	
85 90 95	
cag ttc tcc ctg aac ctg agc tct gtg acc gcc gcg gac acg gcc gtg	336
Gln Phe Ser Leu Asn Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val	
100 105 110	
tac tac tgt gcc aga gat cgg ggc tac ggt gcc agc aat gat gct ttt	384
Tyr Tyr Cys Ala Arg Asp Arg Gly Tyr Gly Ala Ser Asn Asp Ala Phe	
115 120 125	
gat ttc tgg ggc caa ggg ctc agg gtc acc gtc tct tca	423
Asp Phe Trp Gly Gln Gly Leu Arg Val Thr Val Ser Ser	
130 135 140	

<210> 41

<211> 411

<212> DNA

<213> Macaca cynomolgus

<220>

<221> CDS

<222> (1)...(411)

<400> 41

atg aag cac ctg tgg ttc ttc ctc ctc ctg gtg gca act cct aaa tgg 48
 Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Thr Pro Lys Trp
 1 5 10 15

gtc ctg tcc cag gtg cag ttg cat gag tcg ggc cct gga ctg ctg aag 96
 Val Leu Ser Gln Val Gln Leu His Glu Ser Gly Pro Gly Leu Leu Lys
 20 25 30

cct tcg gag acc ctg tcc ctc acc tgc aat gtc tcc ggt gac tcc ccc 144
 Pro Ser Glu Thr Leu Ser Leu Thr Cys Asn Val Ser Gly Asp Ser Pro
 35 40 45

act aag tcc acg tgg aac tgg gtc cgc cag tcc cca ggg aag cca ctg 192
 Thr Lys Ser Thr Trp Asn Trp Val Arg Gln Ser Pro Gly Lys Pro Leu
 50 55 60

gaa tgg att ggt cat gtc ggt tct ggt gga ggt ggc ccc gtt tac aac 240
 Glu Trp Ile Gly His Val Gly Ser Gly Gly Gly Gly Pro Val Tyr Asn
 65 70 75 80

gtc ttc ttg acg ggt cgc gtc tcc atg tct cta gac gct tca aag aag 288
 Val Phe Leu Thr Gly Arg Val Ser Met Ser Leu Asp Ala Ser Lys Lys
 85 90 95

ctt ctc tcc ctg gcc tta gca tct gtg acc gcc gcc gac tcg gcc gtc 336
 Leu Leu Ser Leu Ala Leu Ala Ser Val Thr Ala Ala Asp Ser Ala Val
 100 105 110

42

tat tac tgt gtc aga tcg acg gca tta ttt tcg ttg gat gtc tgg ggc 384
 Tyr Tyr Cys Val Arg Ser Thr Ala Leu Phe Ser Leu Asp Val Trp Gly
 115 120 125

cgg gga ctt ctg gtc acc gtc tcc tca 411
 Arg Gly Leu Leu Val Thr Val Ser Ser
 130 135

<210> 42

<211> 442

<212> DNA

<213> Macaca cynomolgus

<220>

<221> CDS

<222> (1)...(441)

<400> 42

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 Met Glu Leu Gly Leu Ser Trp Val Phe Leu Leu Val Ala Ile Leu Lys
 1 5 10 15

ggg gtc cag tgt gac aag cag ctg gtg cag tcg ggg gga ggc ttg gtc 96
 Gly Val Gln Cys Asp Lys Gln Leu Val Gln Ser Gly Gly Gly Leu Val
 20 25 30

cag cct ggc ggg tct ctg aga ctc gcc tgt gta gcc tcc gga ttc ccc 144
 Gln Pro Gly Gly Ser Leu Arg Leu Ala Cys Val Ala Ser Gly Phe Pro
 35 40 45

ttc agt gac tat tac atg agt tgg gtc cgc cag gct cca ggg aag ggg 192
 Phe Ser Asp Tyr Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly
 50 55 60

ttg gag tgg ctt gga tta att aaa acc aat cct gat ggt gga acg aca 240

Leu Glu Trp Leu Gly Leu Ile Lys Thr Asn Pro Asp Gly Gly Thr Thr
 65 70 75 80

 gat tac gcc gcg tct gtg aaa ggc aga ttt atc atc tca cga gat gat 288
 Asp Tyr Ala Ala Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp
 85 90 95

 tca aag aac tca ctg ttc ctt caa atg aac agc ctg aaa acc gag gac 336
 Ser Lys Asn Ser Leu Phe Leu Gln Met Asn Ser Leu Lys Thr Glu Asp
 100 105 110

 acg gcc gtg tat tac tgc acc aca gaa gtg ttg gtg gtg tct gct att 384
 Thr Ala Val Tyr Tyr Cys Thr Thr Glu Val Leu Val Val Ser Ala Ile
 115 120 125

 caa ctc att gga tgt ctg ggg ccc ggg gag ttg tgg tca ccc gtc tct 432
 Gln Leu Ile Gly Cys Leu Gly Pro Gly Glu Leu Trp Ser Pro Val Ser
 130 135 140

 ttc cgc ttc a 442
 Phe Arg Phe
 145

<210> 43

<211> 407

<212> DNA

<213> Macaca cynomolgus

<220>

<221> CDS

<222> (1) ... (405)

<400> 43

atg aag cac ctg tgg ttc ttc ctc ctc ctg gtg gca gct ccc aga tgg 48
 Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
 1 5 10 15

gtc ctg tcc cag gtg cag ttg gag gag tcg ggc cca gga ctg gtg aag 96
 Val Leu Ser Gln Val Gln Leu Glu Glu Ser Gly Pro Gly Leu Val Lys
 20 25 30

ccc tcg gag acc ctg tcc ctc acc tgc gct gtg tct ggt ggc ctc att 144
 Pro Ser Glu Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Leu Ile
 35 40 45

act gga aac tac tgg aac tgg ctc cgg cag tca gaa ggg aag gga ctg 192
 Thr Gly Asn Tyr Trp Asn Trp Leu Arg Gln Ser Glu Gly Lys Gly Leu
 50 55 60

gag tgg att ggc cat att ggt ggt agt agt ggg aac acc ggc tac aac 240
 Glu Trp Ile Gly His Ile Gly Gly Ser Ser Gly Asn Thr Gly Tyr Asn
 65 70 75 80

tcc gct ttc gag agt cgc gtc acc ttg tca aga gac acg gcc aag aat 288
 Ser Ala Phe Glu Ser Arg Val Thr Leu Ser Arg Asp Thr Ala Lys Asn
 85 90 95

cgg ttc tcc ctg aaa ctg acc tct gtg acc gcc gca gat tcg gcc gtc 336
 Arg Phe Ser Leu Lys Leu Thr Ser Val Thr Ala Ala Asp Ser Ala Val
 100 105 110

tat tac tgt gcg aga tcg ggt ttt acc ggc acc gac ttc ttt tac tat 384
 Tyr Tyr Cys Ala Arg Ser Gly Phe Thr Gly Thr Asp Phe Phe Tyr Tyr
 115 120 125

tgg ggc ccg ggg aag tct tgg tc 407
 Trp Gly Pro Gly Lys Ser Trp
 130 135

<210> 44

<211> 420

<212> DNA

<213> Macaca cynomolgus

<220>

<221> CDS

<222> (1)...(420)

<400> 44

atg aag cac ctg tgg ttc ttc ctc ctc ctg gtg gca gct ccc aga tgg	48
Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp	
1 5 10 15	
gtc ctg tcc cag gtt caa cta cag gag tgc ggc cca gga ctg atg aag	96
Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Met Lys	
20 25 30	
cct tgc gag acc ctg tcc ctc acc tgc gct gtc tct ggt ggc tcc atc	144
Pro Ser Glu Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile	
35 40 45	
agc ggt ggt ttt ggc tgg ggc tgg atc cgt cag tcc ccg ggg aag ggg	192
Ser Gly Gly Phe Gly Trp Gly Trp Ile Arg Gln Ser Pro Gly Lys Gly	
50 55 60	
ctg gaa tgg att gga agt ttc tat act act act gga aat acc ttc tcc	240
Leu Glu Trp Ile Gly Ser Phe Tyr Thr Thr Thr Gly Asn Thr Phe Ser	
65 70 75 80	
aac ccc tcc ctc aag agt cga gtc acc att tca gcg gac acg tcc aag	288
Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Ala Asp Thr Ser Lys	
85 90 95	
aac cag ttc tcc ctg aga ctg acc tct gtg acc gcc gcg gac acg gcc	336
Asn Gln Phe Ser Leu Arg Leu Thr Ser Val Thr Ala Ala Asp Thr Ala	
100 105 110	
gtt tat tac tgt gcg aga gat ctc tat agc agc ggc tat aaa ttt tac	384
Val Tyr Tyr Cys Ala Arg Asp Leu Tyr Ser Ser Gly Tyr Lys Phe Tyr	

115 120 125 420

tac tgg ggc cag gga gtc ctg gtc acc gtc tcc tca

Tyr Trp Gly Gln Gly Val Leu Val Thr Val Ser Ser

130 135 140

<210> 45

<211> 98

<212> PRT

<213> Macaca cynomolgus

<220>

<221> DOMAIN

<222> (31)...(35)

<223> CDRI

<221> DOMAIN

<222> (50)...(66)

<223> CDRII

<400> 45

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly

1 5 10 15

Ser Leu Arg Leu Ala Cys Val Gly Ser Gly Phe Ala Phe Arg Asn Thr

20 25 30

Arg Met His Trp Ile Arg Gln Thr Pro Gly Lys Arg Leu Glu Trp Val

35 40 45

Ala Asp Ile Lys Phe Asp Gly Ser Asp Phe Tyr Tyr Val Asp Ser Val

50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr

65 70 75 80

Leu Glu Met Asn Ser Leu Arg Pro Asp Asp Thr Ala Val Tyr Phe Cys

85 90 95

Val Arg

<210> 46
 <211> 98
 <212> PRT
 <213> Macaca cynomolgus

<220>
 <221> DOMAIN
 <222> (31)...(35)
 <223> CDRI

<221> DOMAIN
 <222> (50)...(66)
 <223> CDRII

<400> 46
 Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
 1 5 10 15
 Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asp Ser Ile Thr Thr Val
 20 25 30
 Phe Trp Ser Trp Leu Arg Gln Ser Pro Gly Ile Gly Leu Glu Trp Ile
 35 40 45
 Gly Asn Phe Ala Gly Ser Thr Pro Glu Thr Asn Tyr Asn Pro Ser Leu
 50 55 60
 Lys Asn Arg Ala Thr Ile Ser Lys Asp Thr Pro Thr Asn Gln Phe Phe
 65 70 75 80
 Leu Arg Leu Thr Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Phe Cys
 85 90 95
 Ala Arg

<210> 47
 <211> 98
 <212> PRT
 <213> Macaca cynomolgus

<220>
 <221> DOMAIN

<222> (31)...(35)

<223> CDRI

<221> DOMAIN

<222> (50)...(66)

<223> CDRII

<400> 47

Glu Val His Leu Val Gln Ser Gly Ala Gln Val Lys Arg Pro Gly Glu
 1 5 10 15
 Ser Leu Arg Ile Ser Cys Lys Thr Ser Gly Tyr Thr Phe Thr Asp Ser
 20 25 30
 Trp Ile Ser Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met
 35 40 45
 Gly Asn Ile Tyr Pro Gly Asp Ser Asp Ser Arg Tyr Asn Pro Ser Phe
 50 55 60
 Gln Gly Arg Val Thr Ile Ser Val Asp Lys Ser Ile Ser Thr Thr Tyr
 65 70 75 80
 Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Thr Tyr Tyr Cys
 85 90 95
 Ala Lys

<210> 48

<211> 98

<212> PRT

<213> Macaca cynomolgus

<220>

<221> DOMAIN

<222> (31)...(35)

<223> CDRI

<221> DOMAIN

<222> (50)...(66)

<223> CDRII

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<210> 49
<211> 98
<212> PRT
<213> Macaca cynomolgus
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<220>  
<221> DOMAIN  
<222> (31)...(35)  
<223> CDRI
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<221> DOMAIN
<222> (50) ... (66)
<223> CDRII
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SUBSTITUTE SHEET (RULE 26)

Gly His Val Gly Ser Gly Gly Gly Gly Pro Val Tyr Asn Val Phe Leu
 50 55 60
 Thr Gly Arg Val Ser Met Ser Leu Asp Ala Ser Lys Lys Leu Leu Ser
 65 70 75 80
 Leu Ala Leu Ala Ser Val Thr Ala Ala Asp Ser Ala Val Tyr Tyr Cys
 85 90 95
 Val Arg

<210> 50
 <211> 100
 <212> PRT
 <213> Macaca cynomolgus

<220>
 <221> DOMAIN
 <222> (31)...(35)
 <223> CDRI

<221> DOMAIN
 <222> (50)...(68)
 <223> CDRII

<400> 50
 Asp Lys Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ala Cys Val Ala Ser Gly Phe Pro Phe Ser Asp Tyr
 20 25 30
 Tyr Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Leu
 35 40 45
 Gly Leu Ile Lys Thr Asn Pro Asp Gly Gly Thr Thr Asp Tyr Ala Ala
 50 55 60
 Ser Val Lys Gly Arg Phe Ile Ile Ser Arg Asp Asp Ser Lys Asn Ser
 65 70 75 80
 Leu Phe Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
 85 90 95
 Tyr Cys Thr Thr

100

<210> 51
 <211> 98
 <212> PRT
 <213> Macaca cynomolgus

<220>
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 <222> (31)...(35)
 <223> CDRI

<221> DOMAIN
 <222> (50)...(66)
 <223> CDRII

<400> 51

Gln Val Gln Leu Glu Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
 1 5 10 15
 Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Leu Ile Thr Gly Asn
 20 25 30
 Tyr Trp Asn Trp Leu Arg Gln Ser Glu Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly His Ile Gly Gly Ser Ser Gly Asn Thr Gly Tyr Asn Ser Ala Phe
 50 55 60
 Glu Ser Arg Val Thr Leu Ser Arg Asp Thr Ala Lys Asn Arg Phe Ser
 65 70 75 80
 Leu Lys Leu Thr Ser Val Thr Ala Ala Asp Ser Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg

<210> 52
 <211> 99
 <212> PRT
 <213> Macaca cynomolgus

<220>

<221> DOMAIN

<222> (31)...(36)

<223> CDRI

<221> DOMAIN

<222> (51)...(67)

<223> CDRII

<400> 52

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Met Lys Pro Ser Glu
 1 5 10 15
 Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Gly Gly
 20 25 30
 Phe Gly Trp Gly Trp Ile Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp
 35 40 45
 Ile Gly Ser Phe Tyr Thr Thr Thr Gly Asn Thr Phe Ser Asn Pro Ser
 50 55 60
 Leu Lys Ser Arg Val Thr Ile Ser Ala Asp Thr Ser Lys Asn Gln Phe
 65 70 75 80
 Ser Leu Arg Leu Thr Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
 85 90 95
 Cys Ala Arg

<210> 53

<211> 390

<212> DNA

<213> Macaca cynomolgus

<220>

<221> CDS

<222> (1)...(390)

<400> 53

atg gac ata agg gtc ccc gtg cag ctc ctg ggg ctc ctg ttg ctc tgg
 Met Asp Ile Arg Val Pro Val Gln Leu Leu Gly Leu Leu Leu Leu Trp

48

1	5	10	15	
ctc cga ggt gcc aga tgt gac atc cag atg acc cag tct cca tcc tcc				96
Leu Arg Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser				
	20	25	30	
ctg tct aca tct gta gga gac act gtc acc atc act tgc cgg gcg agt				144
Leu Ser Thr Ser Val Gly Asp Thr Val Thr Ile Thr Cys Arg Ala Ser				
	35	40	45	
caa ggc att gac acg gag tta gcc tgg tat cag cag aaa cca ggt aaa				192
Gln Gly Ile Asp Thr Glu Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys				
	50	55	60	
gcc ccc aca ctc ctg atc tct gat gcc tcc agg ttg cag acg ggg gtc				240
Ala Pro Thr Leu Leu Ile Ser Asp Ala Ser Arg Leu Gln Thr Gly Val				
	65	70	75	80
tca tct cgg ttc agc ggc agt gga tct gga aca gat ttc act ctc acc				288
Ser Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr				
	85	90	95	
atc aac agc ctg cag cct gaa gat att gcg act tat tac tgt caa cag				336
Ile Asn Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln				
	100	105	110	
gat aat agt ttt cca ctc act ttc ggc gga ggg acc aag gtg gag atc				384
Asp Asn Ser Phe Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile				
	115	120	125	
aaa cga				390
Lys Arg				
	130			

<210> 54

<211> 384

<212> DNA

<213> Macaca cynomolgus

<220>

<221> CDS

<222> (1)...(384)

<400> 54

gtc ttc att tcc ctg ttg ctc tgg atc tct ggt gcc tgt ggg gac att	48
Val Phe Ile Ser Leu Leu Trp Ile Ser Gly Ala Cys Gly Asp Ile	
1 5 10 15	
gtg atg acc cag tct cca gac tcc ctg gct gtg tct ctg gga gag agg	96
Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg	
20 25 30	
gtc acc atc aat tgt aag tcc agc cag agt ctt tta tac agc tcc aac	144
Val Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser Ser Asn	
35 40 45	
aat aag aac tac tta gcc tgg tac cag caa aaa cca gga cag gct cct	192
Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro	
50 55 60	
caa cta ctc att tac tgg gca tct acc cgg gaa tcc ggg gtc cct aat	240
Gln Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asn	
65 70 75 80	
cga ttt agt ggc agc ggc tct ggg aca gat ttc act ctc acc atc agt	288
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser	
85 90 95	
ggc ctg cag gct gaa gat gtg gca gtg tat tac tgt caa cag tat tat	336
Gly Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr	
100 105 110	
gat atg ccc gac agt ttt ggc cag ggg acc aaa gtg gac atc aaa cga	384

55

Asp Met Pro Asp Ser Phe Gly Gln Gly Thr Lys Val Asp Ile Lys Arg
 115 120 125

<210> 55

<211> 399

<212> DNA

<213> Macaca cynomolgus

<220>

<221> CDS

<222> (1)...(399)

<400> 55

atg agg ctc cct gct cag ctc ctg ggg ctg cta ttg ctc tgc gtc ccc 48
 Met Arg Leu Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Cys Val Pro
 1 5 10 15

gga tcc agt ggg gat gtt gtg atg act cag tct cca ctc tcc ctg ccc 96
 Gly Ser Ser Gly Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro
 20 25 30

gtc atc cct gga cag cca gcc tcc atc tcc tgc agg tct agt caa agc 144
 Val Ile Pro Gly Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser
 35 40 45

ctt gta cat agt gac ggg aaa acc tac ttg aat tgg tta caa cag aag 192
 Leu Val His Ser Asp Gly Lys Thr Tyr Leu Asn Trp Leu Gln Gln Lys
 50 55 60

cca ggc caa cct cca aga ctc ctg att tat cag gtt tct aac cgg cac 240
 Pro Gly Gln Pro Pro Arg Leu Leu Ile Tyr Gln Val Ser Asn Arg His
 65 70 75 80

tct ggg gtc cca gac aga ttc agc ggc agt ggg gca ggg aca gac ttc 288
 Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe
 85 90 95

aca ctg aaa atc agc aga gtg gag act gag gat gtt ggg gtt tat tcc 336
 Thr Leu Lys Ile Ser Arg Val Glu Thr Glu Asp Val Gly Val Tyr Ser
 100 105 110

tgc gtg caa ggt aca cac tgg ccg tgg acg ttc ggc caa ggg acc aag 384
 Cys Val Gln Gly Thr His Trp Pro Trp Thr Phe Gly Gln Gly Thr Lys
 115 120 125

gtg gac atc aaa cga 399
 Val Asp Ile Lys Arg
 130

<210> 56

<211> 384

<212> DNA

<213> Macaca cynomolgus

<220>

<221> CDS

<222> (1)...(384)

<400> 56

atg agg gtc ccc gct cag ctc ctg ggg ctc ctg ctg ctc tgg ctc cca 48
 Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp Leu Pro
 1 5 10 15

ggg gcc ata tgt gac att cag atg tcc cag tct cca tcc tcc ctg tct 96
 Gly Ala Ile Cys Asp Ile Gln Met Ser Gln Ser Pro Ser Ser Leu Ser
 20 25 30

gct tct gtg gga gac aga gtc acc atc acc tgc cgg gca agt cag ggc 144
 Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly
 35 40 45

ata act aat tat tta aac tgg tat cag cag aaa ccg ggg aaa gcc cct 192

Ile Thr Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
50 55 60

aac ctc ctg atc tat tat gca act cgt ttg gcg agc ggg gtc cca tca 240
Asn Leu Leu Ile Tyr Tyr Ala Thr Arg Leu Ala Ser Gly Val Pro Ser
65 70 75 80

agg ttc agc ggc agt gga tct ggg tcg gag tac agt ctc gcc atc agc 288
Arg Phe Ser Gly Ser Gly Ser Gly Ser Glu Tyr Ser Leu Ala Ile Ser
85 90 95

agc ctg cag cct gaa gat ttt gca acc tat ttc tgt caa cag ggt tat 336
Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Tyr
100 105 110

agg gcc ccc tac act ttt ggc cag ggg acc aca gtg gag atc aaa cga 384
Arg Ala Pro Tyr Thr Phe Gly Gln Gly Thr Thr Val Glu Ile Lys Arg
115 120 125

<210> 57

<211> 390

<212> DNA

<213> Macaca cynomolgus

<220>

<221> CDS

<222> (1)...(390)

<400> 57

atg gac atg agg gtc ccc gct cag ctc ctg ggg ctc ctg ctg ctc tgg 48
Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

ctc cta ggt gcc aga tgt gac atc cag atg acc cag tct cct tct tcc 96
Leu Leu Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

58

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ttg tct gca tct gta gga gac aga gtc acc atc act tgc caa gcc agt      144
Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Gln Ala Ser
      35              40              45

cag ggt att agc aac tgg tta gcc tgg tat cag cag aaa ccg ggg aaa      192
Gln Gly Ile Ser Asn Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys
      50              55              60

gcc cct aag ctc ctg atc tat gct gca tcc act ttc caa agt ggg gtc      240
Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Thr Phe Gln Ser Gly Val
      65              70              75              80

cca tca agg ttc agc ggc agt gga tct ggg aca gag ttc act ctc acc      288
Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr
              85              90              95

atc agc agc ctg cag cct gaa gat ttt gca act tac tac tgt caa cag      336
Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
              100              105              110

tat aat act tac cct ctc act ttc ggc gga ggg acc aag gtg gag atc      384
Tyr Asn Thr Tyr Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile
              115              120              125

aaa cga      390
Lys Arg
130

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<210> 58

<211> 390

<212> DNA

<213> Macaca cynomolgus

<220>

<221> CDS

<400> 58

60

130

<210> 59
 <211> 88
 <212> PRT
 <213> Macaca cynomolgus

<220>
 <221> DOMAIN
 <222> (24)...(34)
 <223> CDRI

<221> DOMAIN
 <222> (50)...(56)
 <223> CDRII

<400> 59
 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Thr Ser Val Gly
 1 5 10 15
 Asp Thr Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Asp Thr Glu
 20 25 30
 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Thr Leu Leu Ile
 35 40 45
 Ser Asp Ala Ser Arg Leu Gln Thr Gly Val Ser Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Ile Ala Thr Tyr Tyr Cys
 85

<210> 60
 <211> 94
 <212> PRT
 <213> Macaca cynomolgus

<220>

61

<221> DOMAIN

<222> (24) ... (40)

<223> CDRI

<221> DOMAIN

<222> (56) ... (62)

<223> CDRII

<400> 60

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
 1 5 10 15
 Glu Arg Val Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
 20 25 30
 Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
 35 40 45
 Ala Pro Gln Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
 50 55 60
 Pro Asn Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
 65 70 75 80
 Ile Ser Gly Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys
 85 90

<210> 61

<211> 93

<212> PRT

<213> Macaca cynomolgus

<220>

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<223> CDRI

<221> DOMAIN

<222> (54) ... (61)

<223> CDRII

<400> 61

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 1 5 10 15
 Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
 20 25 30
 Asp Gly Lys Thr Tyr Leu Asn Trp Leu Gln Gln Lys Pro Gly Gln Pro
 35 40 45
 Pro Arg Leu Leu Ile Tyr Gln Val Ser Asn Arg His Ser Gly Val Pro
 50 55 60
 Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Lys Ile
 65 70 75 80
 Ser Arg Val Glu Thr Glu Asp Val Gly Val Tyr Ser Cys
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<210> 62

<211> 88

<212> PRT

<213> Macaca cynomolgus

<220>

<221> DOMAIN

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<223> CDRI

<221> DOMAIN

<222> (50)...(56)

<223> CDRII

<400> 62

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 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Thr Asn Tyr
 20 25 30
 Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Asn Leu Leu Ile
 35 40 45
 Tyr Tyr Ala Thr Arg Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Ser Glu Tyr Ser Leu Ala Ile Ser Ser Leu Gln Pro

65 70 75 80
Glu Asp Phe Ala Thr Tyr Phe Cys

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<210> 63

<211> 88

<212> PRT

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<220>

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Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Gly Ile Ser Asn Trp

20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile

35 40 45

Tyr Ala Ala Ser Thr Phe Gln Ser Gly Val Pro Ser Arg Phe Ser Gly

50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro

65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys

85

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<222> (50)...(56)

<223> CDRII

<400> 64

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Asp Thr Val Ser Leu Thr Cys Arg Ala Ser Gln Pro Ile Gly Ser Asn

20 25 30

Leu Asn Trp Phe Gln Gln Lys Pro Gly Ser Pro Pro Arg Leu Leu Ile

35 40 45

Tyr Leu Ala Thr Ala Leu Gln Arg Gly Ile Pro Ser Arg Phe Ser Ala

50 55 60

Thr Gly Ser Gln Thr Asn Phe Thr Leu Thr Ile Thr Gly Leu Gln Pro

65 70 75 80

Glu Asp Phe Ala Thr Tyr Leu Cys

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<210> 65

<211> 360

<212> DNA

<213> Rat

<220>

<221> CDS

<222> (1)...(360)

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48

Asp Thr Val Leu Thr Gln Ser Pro Ala Leu Ala Val Pro Pro Gly Glu

1 5 10 15

65

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agg gtt acc gtc tcc tgt agg gcc agt gaa agt gtc agt aca ttt ttg      96
Arg Val Thr Val Ser Cys Arg Ala Ser Glu Ser Val Ser Thr Phe Leu
      20              25              30

cac tgg tat caa cag aaa cca gga cat caa ccc aaa ctc ctc atc tat      144
His Trp Tyr Gln Gln Lys Pro Gly His Gln Pro Lys Leu Leu Ile Tyr
      35              40              45

cta gcc tca aaa cta gaa tct ggg gtc cct gcc agg ttc agt ggc ggt      192
Leu Ala Ser Lys Leu Glu Ser Gly Val Pro Ala Arg Phe Ser Gly Gly
      50              55              60

ggg tct ggg aca gac ttc acc ctc acc att gat cct gtg gag gct gat      240
Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asp Pro Val Glu Ala Asp
      65              70              75              80

gac act gct acc tat tac tgt cag cag acc tgg aat gat cct cgg acg      288
Asp Thr Ala Thr Tyr Tyr Cys Gln Gln Thr Trp Asn Asp Pro Arg Thr
      85              90              95

ttc ggt gga ggc acc aag ctg gaa ttg aaa cgg gct gat gct gca cca      336
Phe Gly Gly Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp Ala Ala Pro
      100             105             110

act gta tct atc ttc cca cca tcc      360
Thr Val Ser Ile Phe Pro Pro Ser
      115             120

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<210> 66

<211> 360

<212> DNA

<213> Rat

<220>

<221> CDS

<222> (1) ... (360)

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tca gtc aag att tct tgc aag gct tct ggc tac acc ttt aca gat tac	96
Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr	
20 25 30	
gtt ttg aat tgg gtg aag cag agt cct gga cag gga ctg gaa tgg ata	144
Val Leu Asn Trp Val Lys Gln Ser Pro Gly Gln Gly Leu Glu Trp Ile	
35 40 45	
gga tgg att gat cct gac tat ggt act act gat tat gct gag aag ttc	192
Gly Trp Ile Asp Pro Asp Tyr Gly Thr Thr Asp Tyr Ala Glu Lys Phe	
50 55 60	
aaa aag aag gcc aca ctg act gca gat aca tcc tcc agc aca gcc tac	240
Lys Lys Lys Ala Thr Leu Thr Ala Asp Thr Ser Ser Ser Thr Ala Tyr	
65 70 75 80	
atc cag ctt agc agc ctg aca tct gag gac aca gcc acc tat ttt tgt	288
Ile Gln Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Thr Tyr Phe Cys	
85 90 95	
gct aga tct agg aat tac gga gga tat att aat tac tgg ggc caa gga	336
Ala Arg Ser Arg Asn Tyr Gly Gly Tyr Ile Asn Tyr Trp Gly Gln Gly	
100 105 110	
gtc atg gtc aca gtc tcc tca gct	360
Val Met Val Thr Val Ser Ser Ala	
115 120	

<210> 67

<211> 109

<212> PRT

<213> Pan troglodytes

<400> 67

Ala Val His Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15
 Asp Ser Val Thr Ile Thr Cys Arg Ala Ser Gln Thr Ile Asn Ile Tyr
 20 25 30
 Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Phe Asp Ala Ser Ile Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Ser Leu Thr Ile Arg Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Cys Gly Trp Gly Thr His Pro
 85 90 95
 Tyr Asn Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
 100 105

<210> 68

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> rat/chimpanzee sequence

<400> 68

Asp Thr Val Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15
 Asp Ser Val Thr Ile Thr Cys Arg Ala Ser Glu Ser Val Ser Thr Phe
 20 25 30
 Leu His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Leu Ala Ser Lys Leu Glu Ser Gly Val Pro Ala Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Ser Leu Thr Ile Arg Ser Leu Gln Pro

68

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<210> 69
<211> 128
<212> PRT
<213> Pan troglodytes
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<210> 70
<211> 118
<212> PRT
<213> Artificial Sequence
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<220>

<223> rat/chimpanzee sequence

<400> 70

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
 20 25 30
 Val Leu Asn Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
 35 40 45
 Gly Trp Ile Asp Pro Asp Tyr Gly Thr Thr Asp Tyr Ala Glu Lys Phe
 50 55 60
 Lys Lys Lys Ala Thr Leu Ser Ala Asp Thr Ser Arg Asn Ser Ala Tyr
 65 70 75 80
 Leu Gln Met Asn Asp Leu Arg Pro Glu Asp Thr Ala Ile Tyr Phe Cys
 85 90 95
 Ala Arg Ser Arg Asn Tyr Gly Gly Tyr Ile Asn Tyr Trp Gly Gln Gly
 100 105 110
 Thr Leu Val Thr Val Ser
 115

<210> 71

<211> 354

<212> DNA

<213> Murine

<220>

<221> CDS

<222> (1)...(354)

<400> 71

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 1 5 10 15
 tca gtg aag ata tcc tgc aag gct act ggc tac aca ttc agt agc tac 96
 Ser Val Lys Ile Ser Cys Lys Ala Thr Gly Tyr Thr Phe Ser Ser Tyr
 20 25 30
 tgg ata gag tgg gta aag cag agg cct gga cat ggc ctt gag tgg att 144

70

Trp Ile Glu Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp Ile
 35 40 45
 gga gag att tta cct aga agt ggt aat act aac tac aat gag aag ttc 192
 Gly Glu Ile Leu Pro Arg Ser Gly Asn Thr Asn Tyr Asn Glu Lys Phe
 50 55 60
 aag ggc aag gcc aca ttc act gca gaa aca tcc tcc aac aca gcc tac 240
 Lys Gly Lys Ala Thr Phe Thr Ala Glu Thr Ser Ser Asn Thr Ala Tyr
 65 70 75 80
 atg caa ctc agc agc ctg aca cct gag gac tct gcc gtc tat tac tgt 288
 Met Gln Leu Ser Ser Leu Thr Pro Glu Asp Ser Ala Val Tyr Tyr Cys
 85 90 95
 tca agt cgc ggc gtc agg ggc tct atg gac tac tgg ggt caa gga acc 336
 Ser Ser Arg Gly Val Arg Gly Ser Met Asp Tyr Trp Gly Gln Gly Thr
 100 105 110
 tca gtc acc gtc tcc tca 354
 Ser Val Thr Val Ser Ser
 115

<210> 72

<211> 324

<212> DNA

<213> Murine

<220>

<221> CDS

<222> (1)...(324)

<400> 72

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 1 5 10 15

gac aga gtc acc atc act tgc agg tca agt cag gac att agc aat ttt 96
 Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Asp Ile Ser Asn Phe
 20 25 30

tta aac tgg tat cag cag aaa cca gat gga act gtt aaa ctc ctg atc 144
 Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
 35 40 45

tac tac aca tca aca tta cac tca gga gtc cca tca agg ttc agt ggc 192
 Tyr Tyr Thr Ser Thr Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

agt ggg tct gga aca gat tat tct ctc acc att agc aac ctg gag caa 240
 Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln
 65 70 75 80

gaa gat att gcc act tac ttt tgc caa cag ggt aat acg ctt cct tgg 288
 Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Trp
 85 90 95

acg ttc ggt gga ggc acc aac ctg gaa atc aaa cgg 324
 Thr Phe Gly Gly Gly Thr Asn Leu Glu Ile Lys Arg
 100 105

<210> 73

<211> 108

<212> PRT

<213> Artificial Sequence

<220>

<223> murine/chimpanzee sequence

<400> 73

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 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Asp Ile Ser Asn Phe
 20 25 30
 Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Tyr Thr Ser Thr Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Asn Thr Leu Pro Trp
 85 90 95
 Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> 74

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> murine/chimpanzee sequence

<400> 74

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Ser Tyr
 20 25 30
 Trp Ile Glu Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
 35 40 45
 Gly Glu Ile Leu Pro Arg Ser Gly Asn Thr Asn Tyr Asn Glu Lys Phe
 50 55 60
 Lys Gly Lys Ala Ser Phe Asn Ala Asp Thr Ser Thr Asn Ile Ala Tyr
 65 70 75 80
 Met Glu Leu Thr Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ser Ser Arg Gly Val Arg Gly Ser Met Asp Tyr Trp Gly Gln Gly Thr
 100 105 110
 Leu Val Thr Val Ser Ser

115

<210> 75

<211> 360

<212> DNA

<213> Murine

<220>

<221> CDS

<222> (1)...(360)

<400> 75

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1 5 10 15	
tca gtg aag ctg tcc tgc aag gct tct ggc agt acc ttc acc agc tac	96
Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Ser Thr Phe Thr Ser Tyr	
20 25 30	
tgg atg cac tgg gtg aag cag agg cct gga cga ggc ctt gag tgg att	144
Trp Met His Trp Val Lys Gln Arg Pro Gly Arg Gly Leu Glu Trp Ile	
35 40 45	
gga agg att gat cca aat agt ggt ggt act aag gat aat gag aag ttc	192
Gly Arg Ile Asp Pro Asn Ser Gly Gly Thr Lys Asp Asn Glu Lys Phe	
50 55 60	
aag agc aag gcc aca ctg act gta gac aaa ccc tcc agc aca gcc tac	240
Lys Ser Lys Ala Thr Leu Thr Val Asp Lys Pro Ser Ser Thr Ala Tyr	
65 70 75 80	
atg cag ctc agc agc ctg aca tct gag gac tct gcg gtc tat tat tgt	288
Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys	
85 90 95	
gca aga gag acc tac tat gat tcc tcg ttt gct tac tgg ggc caa ggg	336

74

Ala Arg Glu Thr Tyr Tyr Asp Ser Ser Phe Ala Tyr Trp Gly Gln Gly
 100 105 110

act ctg gtc act gtc tct gca gcc 360
 Thr Leu Val Thr Val Ser Ala Ala
 115 120

<210> 76

<211> 336

<212> DNA

<213> Murine

<220>

<221> CDS

<222> (1)...(336)

<400> 76

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gac agg gtc agc gtc acc tgc aag gcc agt cag aat gtg ggt act aat 96
 Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val Gly Thr Asn
 20 25 30

gta gcc tgg tat caa cag aaa cca ggg caa tct cct aaa gca ctg att 144
 Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Ala Leu Ile
 35 40 45

tac tcg gca tcc tac cgg tac agt gga gtc cct gat cgc ttc aca ggc 192
 Tyr Ser Ala Ser Tyr Arg Tyr Ser Gly Val Pro Asp Arg Phe Thr Gly
 50 55 60

agt gga tct ggg aca gat ttc act ctc acc atc agc aat gtg cag tct 240
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser
 65 70 75 80

75

gaa gac ttg gca gag tat ttc tgt cag caa tat aac agc tat cct ctc 288
 Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
 85 90 95

acg ttc ggt gct ggg acc aag ctg gag ctg aaa cgg gct gat gct gca 336
 Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp Ala Ala
 100 105 110

<210> 77

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> murine/chimpanzee sequence

<400> 77

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 20 25 30
 Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Ala Leu Ile
 35 40 45
 Tyr Ser Ala Ser Tyr Arg Tyr Ser Gly Val Pro Asp Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
 85 90 95
 Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105

<210> 78

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> murine/chimpanzee sequence

<400> 78

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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Ser Thr Phe Thr Ser Tyr
           20           25           30
Trp Met His Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
           35           40           45
Gly Arg Ile Asp Pro Asn Ser Gly Gly Thr Lys Asp Asn Glu Lys Phe
           50           55           60
Lys Ser Lys Ala Thr Leu Asn Val Asp Lys Ser Thr Asn Ile Ala Tyr
65           70           75           80
Met Glu Leu Thr Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
           85           90           95
Ala Arg Glu Thr Tyr Tyr Asp Ser Ser Phe Ala Tyr Trp Gly Gln Gly
           100          105          110
Thr Met Val Thr Val Ser
           115

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<210> 79

<211> 119

<212> PRT

<213> Artificial Sequence

<220>

<223> murine/human sequence

<400> 79

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
 1           5           10           15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Ser Thr Phe Thr Ser Tyr
           20           25           30
Trp Met His Trp Val Lys Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile

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35 40 45
 Gly Arg Ile Asp Pro Asn Ser Gly Gly Thr Lys Asp Asn Glu Lys Phe
 50 55 60
 Lys Ser Lys Ala Thr Leu Thr Val Asp Lys Ser Thr Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Glu Thr Tyr Tyr Asp Ser Ser Phe Ala Tyr Trp Gly Gln Gly
 100 105 110
 Thr Met Val Thr Val Ser Ala
 115

<210> 80

<211> 102

<212> PRT

<213> Artificial Sequence

<220>

<223> murine/human sequence

<400> 80

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asn Val Gly Thr Asn
 20 25 30
 Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Ala Leu Ile
 35 40 45
 Tyr Ser Ala Ser Tyr Arg Tyr Ser Gly Val Pro Asp Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
 85 90 95
 Thr Phe Gly Gly Gly Thr
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<210> 81

<211> 11

<212> PRT

<213> Pan troglodytes

<400> 81

Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser

1 5 10

<210> 82

<211> 11

<212> PRT

<213> Pan troglodytes

<400> 82

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser

1 5 10

<210> 83

<211> 11

<212> PRT

<213> Pan troglodytes

<400> 83

Trp Gly Pro Gly Thr Leu Val Thr Val Ser Ser

1 5 10

<210> 84

<211> 11

<212> PRT

<213> Pan troglodytes

<400> 84

Trp Gly Gln Gly Ile Leu Val Thr Val Ser Ser

1 5 10

<210> 85

<211> 11

<212> PRT

<213> Pan troglodytes

<400> 85

Trp Gly Arg Gly Ile Leu Val Ile Val Ser Ser

1 5 10

<210> 86

<211> 11

<212> PRT

<213> Pan troglodytes

<400> 86

Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg

1 5 10

<210> 87

<211> 11

<212> PRT

<213> Pan troglodytes

<400> 87

Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg

1 5 10

<210> 88

<211> 11

<212> PRT

<213> Macaca cynomolgus

<400> 88

Trp Gly Arg Gly Val Leu Val Thr Val Ser Ser

1 5 10

<210> 89

<211> 11

<212> PRT

<213> Macaca cynomolgus

<400> 89

Trp Gly Gln Gly Val Gln Val Thr Val Ser Ser

1 5 10

<210> 90

<211> 11

<212> PRT

<213> Macaca cynomolgus

<400> 90

Trp Gly Pro Gly Val Met Val Thr Val Ser Ser

1 5 10

<210> 91

<211> 11

<212> PRT

<213> Macaca cynomolgus

<400> 91

Trp Gly Arg Gly Leu Leu Val Thr Val Ser Ser

1 5 10

<210> 92

<211> 11

<212> PRT

<213> Macaca cynomolgus

<400> 92

Trp Gly Gln Gly Val Leu Val Thr Val Ser Ser

1 5 10

<210> 93

<211> 11

<212> PRT

<213> Macaca cynomolgus

<400> 93

Trp Gly Gln Gly Leu Arg Val Thr Val Ser Ser

1 5 10

<210> 94

<211> 11

<212> PRT

<213> Macaca cynomolgus

<400> 94

Phe Gly Gln Gly Thr Lys Val Asp Ile Lys Arg

1 5 10

<210> 95

<211> 11

<212> PRT

<213> Macaca cynomolgus

<400> 95

Phe Gly Gln Gly Thr Thr Val Glu Ile Lys Arg

1 5 10

<210> 96

<211> 11

<212> PRT

<213> Macaca cynomolgus

<400> 96

Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg

1 5 10

<210> 97

<211> 11

<212> PRT

<213> Pan troglodytes

<400> 97

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg

1

5

10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/09131

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 39/395

US CL : 530/387.3; 424/133.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/387.3; 424/133.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

none

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, Medline, Biosis

search terms: immunoglobulin, antibody, framework regions, CDR grafted, humanized, primatized

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ANDERSON et al. A primatized MAb to Human CD4 causes receptor modulation without marked reduction in CD4+ T cells in Chimpanzees: In vitro and in vivo characterization of a MAb (IDEC-CE9.1) to human CD4. Clinical Immunology and Immunopathology. July 1997, Vol. 84, No. 1, pages 73-84, see entire document.	1-19



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

26 JULY 1999

Date of mailing of the international search report

18 AUG 1999

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

JULIE BURKE

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/09131

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 20-31
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

the claim contain specific sequence identification numbers however the application has not complied with the sequence requirements.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.